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Patent Analysis for Medicines and Biotherapeutics in Trials to Treat COVID-19

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RESEARCH PAPER

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PATENT ANALYSIS FOR MEDICINES AND BIOTHERAPEUTICS IN TRIALS TO TREAT COVID-19

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SOUTH CENTRE

26 APRIL 2022

^{*} This analysis was conducted by Ms. Srividya Ravi, Consultant and Patent Agent in India.

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ABSTRACT

This report provides an analysis of patents covering medicines in trials to treat COVID-19. The aim of the report is to support national patent offices and interested parties in developing countries with information that can serve as guidance for the examination of the claims contained in relevant patents or patent applications.

The medicines considered for the patent analysis in this report are remdesivir, ruxolitinib, favipiravir, molnupiravir and nirmatrelvir, and the biotherapeutics tocilizumab, siltuximab and sarilumab.

Este informe proporciona un análisis de las patentes que cubren los medicamentos que se encuentran en ensayos clínicos para el tratamiento de COVID-19. El objetivo del informe es apoyar a las oficinas nacionales de patentes y demás partes interesadas de los países en desarrollo con información que pueda servir de orientación para el examen de las reivindicaciones contenidas en las patentes o solicitudes de patente pertinentes.

Los medicamentos considerados para el análisis de las patentes en este informe son remdesivir, ruxolitinib, favipiravir, molnupiravir y nirmatrelvir, y los bioterapéuticos tocilizumab, siltuximab y sarilumab.

Ce rapport fournit une analyse des brevets couvrant les médicaments en cours d'essai pour traiter le COVID-19. Le but du rapport est de fournir aux offices nationaux des brevets et d'autres parties intéressées dans les pays en développement des informations qui pourraient être utiles pour l'examen des revendications des brevets ou pour l'examen d'une demande de brevet.

Les médicaments considérés pour l'analyse des brevets dans ce rapport sont le remdesivir, le ruxolitinib, le favipiravir, le molnupiravir et le nirmatrelvir, ainsi que les produits biothérapeutiques tocilizumab, siltuximab et sarilumab.

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LIST OF ACRONYMS

CDR	complementary determining region
COVID-19	Infectious disease caused by the SARS-CoV-2 virus
EBV	Epstein Barr virus
EC50	Half maximal effective concentration
EPO	European Patent Office
EU	European Union
FDA	US Food and Drug Administration
FR	France
HCV	hepatitis C virus
HHV-8	human herpesvirus-8
HIV	human immunodeficiency virus
HPV	human papilloma virus
HTLV 1	human T-cell leukemia virus type 1
IC50	half maximal inhibitory concentration
IgG1	Immunoglobulin G1
IL-6	interleukin-6
IL-6R	Interleukin-6 receptor
iMCD	idiopathic multicentric Castleman's disease
IN	India
IPRP	International Preliminary Report on Patentability
ISR	International Search Report
IUPAC	International Union of Pure and Applied Chemistry
JAK	Janus kinases
K _D	Refers to the affinity of the antibody to the receptor
mM	millimolar
–NH ₂ group	compounds and functional groups that contain a basic nitrogen atom with a lone pair
nM	nanomolar
P	Phosphorus
PCT	Patent Cooperation Treaty
pM	picomolar

μM	micromolar
UNDP	United Nations Development Programme
US	United States
USPTO	United States Patent and Trademark Office
VZV	Varicella-zoster virus
WO	Prefix indicating a patent filling under the Patent Cooperation Treaty administered by WIPO
WIPO	World Intellectual Property Organization

INTRODUCTION

This report provides an analysis of patents covering medicines in trials to treat COVID-19. The aim of the report is to support national patent offices and interested parties in developing countries with information that can serve as guidance for the examination of the claims contained in relevant patents or patent applications.

The medicines considered for the patent analysis in this report are remdesivir, ruxolitinib, favipiravir, molnupiravir and nirmatrelvir, and the biotherapeutics tocilizumab, sarilumab and siltuximab.

The report examines the admissibility of the claims contained in patent applications or granted patents for a number of medicines under study in the light of rigorous patentability standards. The guiding criteria used to examine such admissibility are based on the “Guidelines for the examination of patent applications relating to pharmaceuticals”, UNDP 2016 (hereinafter referred to as ‘Guidelines’).² The analysis addresses the technical aspects of the patent specifications and claims, described in a manner that is readable for a non-expert, including possible grounds for the amendment or rejection of the claimed invention.

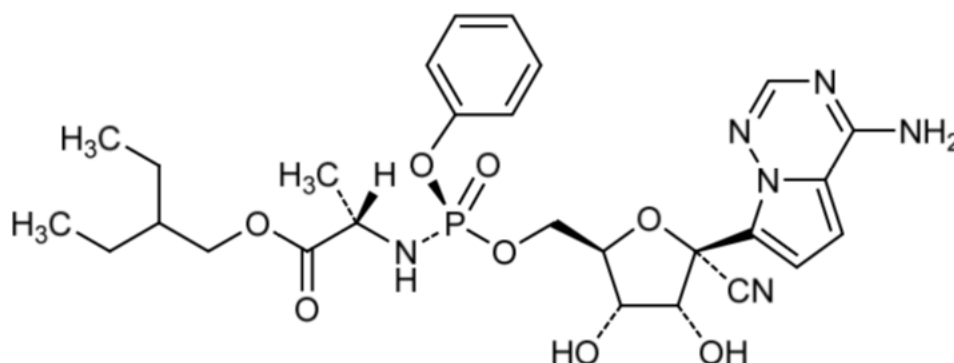
The methodology applied for preparing this report was as follows: the patent applications and the claims of the respective patents granted by the Indian Patent Office, the United States United States Patent and Trademark Office (USPTO) and by the European Patent Office (EPO) were studied, as well as the International Search Report (ISR) and Written Opinion of patent applications filed under the Patent Cooperation Treaty (PCT). The prosecution history of the patent applications at international stage (WO filing) and national phase (India, United States and Europe) were analyzed. A comparative analysis of claims in the various patent applications and eventually granted claims were also made. The patent specification and claims were critically examined for disclosure, enablement and other patentability requirements and a detailed claim analysis was conducted. The compliance to the basic tenets of patenting, and to the referred to Guidelines was evaluated. Accordingly, key findings were enlisted. If required, a brief prior art search was also conducted, and the identified documents studied.

² Available from <https://www.undp.org/content/undp/en/home/librarypage/hiv-aids/guidelines-for-the-examination-of-patent-applications-relating-t.html>.

REMDESIVIR

Background

Remdesivir is a broad spectrum anti-viral drug developed and patented by Gilead Sciences in nearly 70 countries. It is administered by parenteral route (injection) to relieve subjects of viral infections.



Molecular formula: $C_{27}H_{35}N_6O_8P$

IUPAC name: (2S)-2-[(2R,3S,4R,5R)-[5-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxy-tetrahydro-furan-2-ylmethoxy]phenoxy-(S)-phosphorylamino]propionic acid 2-ethyl-butyl ester

Patents Studied

WO2009132135. Filed on 22 April 2009.

WO2012012776. Filed on 22 July 2011.

WO2016069826. Filed on 29 October 2015.

WO2017049060. Filed on 16 September 2019.

WO2009132135

WO2009132135 is a patent application that covers a broad Markush³ structure and its pharmaceutically acceptable salts i.e., Compound of Formula I that can potentially protect millions of compounds. The patent specification has disclosed the synthesis of mere 44 compounds and the characterization data for only 13 compounds are included.

Several compounds and preferred substituents at various positions in the core ring are provided and claimed; however, Remdesivir is not explicitly disclosed in this application. It is

³ A Markush claim is a particular kind of patent claim that lists alternative species or elements that can be selected as part of the claimed invention.

not one of the preferred embodiments of the compound of formula I, but remdesivir is broadly covered in the claims.

Some embodiments of the compounds are close to the chemical structure of remdesivir, but the exact compound is covered remotely, and not disclosed explicitly and particularly. Few Compounds that are very close to Remdesivir are those of e.g., 21 and 26, refer pages 135 and 137. Claim 18 claims particular compounds of Claim 1, around 36 compounds are disclosed, few have no P, few have more than one P, some do not have the group $C\equiv N$, remdesivir is not one of them.

Up to claim 18, the compound is claimed. Claim 19 includes a racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph or amorphous form.

Claims 20-22 is for a pharmaceutical composition alone or in combination with other therapeutic agents, including agents to treat Hepatitis C viruses (HCV) and interferons.

Claims 23-28 are method claims for inhibiting HCV polymerase and treating a viral infection caused by a virus of the Flaviviridae family including Dengue and Hepatitis C viruses amongst many other infections, alone or in combination with other agents.

Claim 29 pertains to a compound as in any one of claims 1 to 18 used in the manufacture of a medicament for treating a viral infection caused by a virus.

Regarding anti-viral activity, a general protocol has been provided. Also, protocols for cell-based EC₅₀ and Cytotoxicity assay is provided, but no results are enlisted. The anti-viral study has been conducted on mouse model for dengue infection and a generic conclusion has been arrived at. There are no results for assay of even the few compounds (44) synthesized. There is also no result with regard to subject group and control group.

The IC₅₀ for HCV by NS5b polymerase assay lists results as <100 μ M, <10 μ M and for compound 17 as < 1 μ M. For the seven compounds for which EC₅₀ results have been shared, one compound was < 1 μ M, 2 were 1-10 μ M and four were 10-100 μ M. None of these seven compounds were Remdesivir.

Results of cytotoxicity tests are not disclosed.

To establish inventive step for EPO, following data was provided:

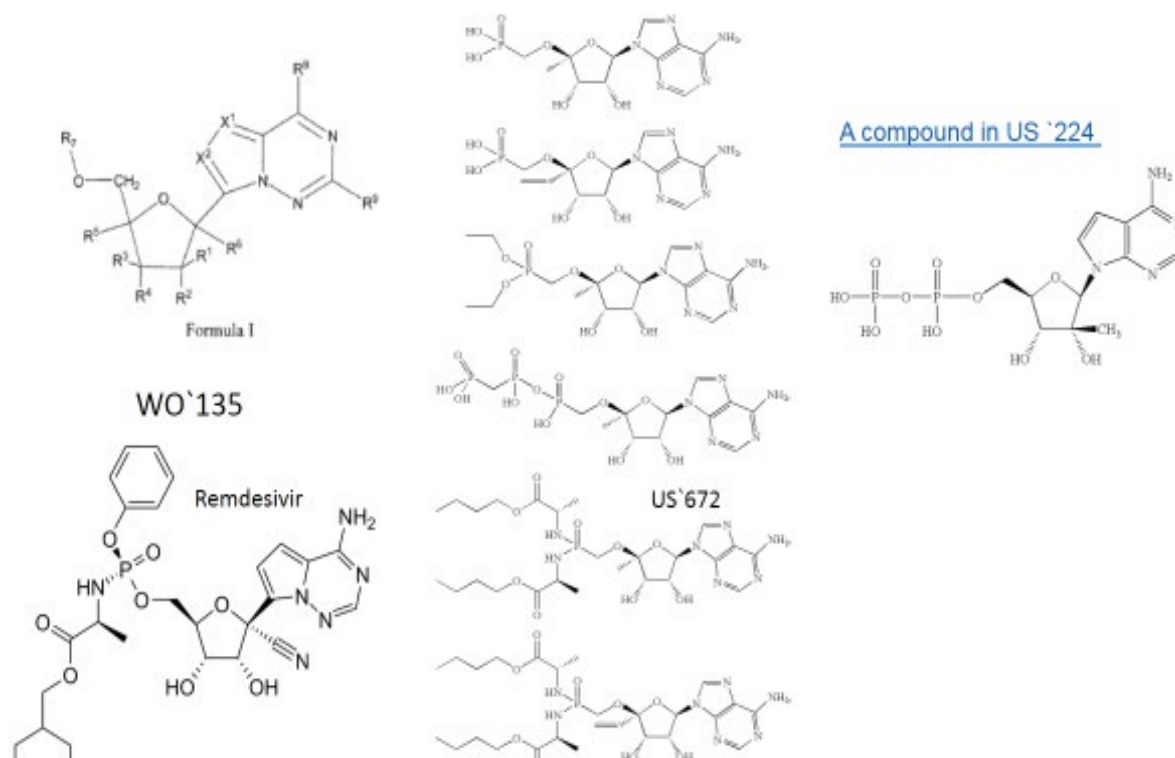
Moreover, in the following table exact values for the same compounds are given:

Compound No.	EC ₅₀ μ M
2	24
3	33
4	>89
5	55
6	0.7
12	5.5
13	4.8

Since the Examining Division already acknowledged an inventive step in case exact data are provided, it is believed that no further comments with regard to an inventive step are required.

Activity specifically for seven compounds was provided and EPO processed a grant.

While the compounds disclosed may be novel, the compounds are a combination of two relevant prior arts, US 7842672 filed on 6 July 2007 by Gilead and US 7202224 filed on 31 July 2006 by Merck. Very closely related compounds are disclosed and they also possess anti-viral activity and are useful for treating various viral infections. US 7202224 claims a method of treating an infection caused by HCV, while US 7842672 is also used to treat viral infections, alone and in combination with other therapeutic agents.



Referring to the image above, compounds with nitrogen (N) and oxygen (O) containing rings and P=O and it being further substituted are known prior to the WO2009132135 patent for anti-viral activity itself. The Indian Patent Office has cited these two documents in its Examination report and accordingly claims were amended to move away from the citations. However, neither for the cited compounds nor for the invention's compound is activity studied in detail and disclosed.

Note: Referring to the image, as you view it, the right most panel lists the US 7202224 compound. The rings right most in the structure has three N and one –NH₂ group. In the middle panel are compounds of another prior art, US 7842672. The rings contain four N and the –NH₂ group. Remdesivir and its patent WO2009132135 (refer left most panel) also have the –NH₂ group and rings of same structure, but with three N in different positions.

Referring to the P=O group on the left side of the different structures, all the molecules possess P=O group, but other groups are differently linked to P. The ring with O is common and the O group out of this ring linking to P=O directly or through one –CH is also common. Further groups on P however differ.

The two cited documents also refer to compounds with anti-viral activity and most parts of the structure that possibly play key roles in eliciting the said activity seem to be disclosed. So,

Remdesivir and compounds of formula I of WO2009132135 are bound to possess anti-viral activity and thus are obvious.

Summary of Observations

- The WO2009132135 patent claims a Markush structure which covers at least thousands if not millions of compounds.
- While remdesivir is covered by the Markush, it is not enabled and particularly disclosed in this application.
- The process and synthesis is provided for mere 44 compounds, and fewer compounds are characterized.
- None of the test results for anti-viral activity or toxicity studies are provided in detail. Just 8 compounds have been assessed for anti-viral activity.
- The compounds are highly obvious in light of two cited documents US 7842672 and US 7202224.

Key Findings

1. WO2009132135 lacks preferred embodiment description for remdesivir.
2. The compound is neither described, nor its process of synthesis described, nor is it characterized, nor is it evaluated for anti-viral activity.
3. The activity of remdesivir against Flaviviridae family of viruses is not demonstrated in this invention.
4. The patent demonstrates a few compounds to possess anti-viral activity and covers a huge number of possible anti-viral drug candidates.
5. Such possible compounds may be limited to the extent covered in prior arts, if they are demonstrated to show unexpectedly potent anti-viral activity, given that prior arts demonstrate similar compounds for the same activity.

Status of national phase applications:

US 8012941-granted in 2011 no significant update in the file.

US 8008264-Allowed in 2011. Gilead, the Applicant has filed for a patent term extension under sec 156 of USC in accordance with USPTO announcement in May 2020 that the COVID-19 outbreak is an extra-ordinary situation. Earlier the case had a patent term adjustment under Sec 154 for 198 days. 6 September 2029 is date of expiry. On 17 December 2020 Gilead has applied for a patent term extension under Sec 156 of 35 USC. There are no further significant updates in the file.

US 8318682-granted in 2012. In Dec 2020, Applicant has applied for patent term extension under Sec 156, no further significant updates in the file.

US8853171 granted in 2014. No significant update in file.

US RE46762 granted in 2018, Applicant has applied for patent term extension under Sec 156 in Dec 2020, no further significant updates in the file.

EP2937350 granted in 2017, no significant update on file, period to file opposition has expired, and EP2280973 a Markush and few specific compounds and use of compounds to treat viruses, particularly Hep C and Zika virus.

EP2268642 granted in 2015, no significant update on file, period to file opposition has expired. This patent has the broadest coverage, a Markush, compositions, method and uses.

EP2280973- granted in 2012, no significant update on file, period to file opposition has expired.

At KPO also, there seems to be an application for term extension dated 23 October 2020.

JP application was withdrawn in 2015.

WO2012012776

This is a narrower version of WO2009132135 and claims the compound of formula I or its salt or ester for use in treating a paramyxoviridae infection.

This is essentially a use claim, not allowed in many countries.

The scope is a little limited in terms of compounds covered in comparison to WO2009132135, however in terms of claim coverage, it is a use claim. Remdesivir is explicitly claimed with structure listed in claim 13 with its salts, also refer compound 9 on page 127 – for synthesis and characterization. Pharmaceutical composition, combination with many drugs, administration by inhalation or nebulization (claims 17 and 18) and use against many viruses including parainfluenza, pneumonia, inhibition of Paramyxoviridae polymerase (claim 24) are all covered.

Examples for synthesis and characterization for 20 compounds provided. Organic, inorganic and amino acid addition salts are described, so are enantiomers and diastereomers.

Tablet formulations, eye formulations emulsions are all described with acceptable excipients. Other solid and liquid dosage forms are also described including emulsions, powders, and topical and inhaling formulations are covered. Nebulizing formulation and dry powder inhalation also disclosed. Parenteral, vaginal, rectal, and controlled release profiles also disclosed. Combinations with a huge number of drugs is covered and metabolites of the drug are described.

Activity data for few compounds provided, just 5-10, however, remdesivir does not seem to be evaluated for activity against paramyxoviridae infection.

Status of national phase applications:

US 13/189273 and US 14/579348- are abandoned in 2015 and 2017 respectively due to non-reply to Office action.

US10065958 -granted in 2018, no significant update on file, one compound and its salt or ester is allowed, which is remdesivir.

US 16/879491-Filed in May 2020, is ready for examination.

US 10696679-Granted in 2020, no significant update on file-A method to treat paramyxoviridae family of viruses using remdesivir and in combination with other agents is allowed.

EP 2595980- granted in 2014, no significant update on file, period to file opposition has expired. Claims a broad Markush for use in treating paramyxoviridae infections, compositions, combinations with other agents and focuses predominantly on paramyxoviridae family of viruses. Particularly a fair number of specific compounds are

claimed, including remdesivir. A later claim to a Markush with specific compounds is also included with no limitation of a particular use.

WO2016069826

The WO2016069826 patent application is titled “Methods for Treating Filoviridae Virus Infections”. It contains 24 claims. The first independent claim is a method of treating filoviridae infection in humans with compound of formula IV where option to only one substituent, R7, is retained and its salts and hydrates and esters are included. The options for R7 are very large and a huge number of compounds are possible. Particular substituents of remdesivir are claimed in claims 3 and 4. The diastereomers are listed in Claim 5 and 6 and claim 7 particularly covers remdesivir.

Claim 8 claims a carrier and excipient, 9 and 10 claim combination with few monoclonal antibodies, Ebola convalescent plasma, favipiravir and few more drugs. Claims 11-14 cover various viruses of the filoviridae type, and particularly Ebola is claimed.

Claim 16 is a compound claim and 17 compounds are listed. Claim 17 claims remdesivir in particular. Claim 18 claims compositions. Claims 19,20 and 21 claim a compound to treat filoviridae and claims 22-24 are use claims or Swiss claims.

The patent specification covers oral, parenteral, ophthalmic, rectal, veterinary, nasal buccal and sublingual formulations and for treatment ranging from 1-100 days. Combinations with various classes of drugs are also covered. The method of treatment is by inhibiting filoviridae polymerase, and assay for the same has been performed. Around 30 compounds and few salts and stereoisomers have been exemplified for synthetic procedure as well as characterized.

Biological assay: The protocols followed for the anti-viral assays and the evaluation of the compounds for their activity is provided. Few compounds were tested and the results for Remdesivir (i.e., Compound 32) in comparison to its diastereomer (Compound 9) are provided. The activity is evaluated for Ebola, Nipah and Marburg viruses in particular.

Summary of observations

The Markush potentially covers hundreds of compounds. Just around 15 compounds and their salts and diastereomers are synthesized, and only few exhibit activity against the filoviridae virus. Based on such data, a method claim is granted over the entire Markush structure.

The method of treating Filoviridae is novel, since prior arts disclose the use of same or similar compounds against other viruses. Having known that similar compounds can be used to treat viruses such as hepatitis C, influenza, paramyxoviridae and so on, the challenge in using the particular diastereomer for treating filoviridae seems to be a matter of routine experimentation. If not, the onus is on the applicant to bring out the challenge in identifying remdesivir to treat filoviridae infections, in light of prior arts for various types of viruses.

Regarding the compound claims, the claim for remdesivir lacks novelty in view of the explicit disclosure in WO2012012776. The WO2012012776 patent application discloses a diastereomer that is different from the one claimed in the current case and also the one that exhibits activity against filoviridae viruses. But referring to the guidelines, particularly pages 30-32, which states that enantiomers are inherently anticipated and obvious to try when evaluated for inventive step, the compound claims lack novelty and inventive step.

However, the equivalent patent is granted in several countries including US, EPO, India and so on. In India, a patent for selected compounds, including and specifically remdesivir has been granted in IN332280, since method of treatment and use claims are not allowed in India. The patent was voluntarily licensed by Gilead to several Indian pharmaceutical companies for combatting the COVID-19 pandemic. A post-grant opposition against the granted patent has been filed citing the WO2009132135 and WO2012012776 as affecting the novelty of the compound claims. A reply to the notice of the post grant opposition has been recently filed by Gilead and it states that the patent claims the diastereomer that is not explicitly disclosed in the prior arts, including WO2012012776 patent, and for a prior art to be affecting the novelty, it should disclose all elements of the invention. Further, the rebuttal to the opposition notice states that none of the prior arts suggest that this particular compound and the particular diastereomer can be efficacious against filoviridae viruses. No further update on the status of the opposition is available.

Similar arguments were also provided to overcome the comments in the FER and objections raised on the basis of Sec 3 (d) of the Indian Patent Act.

Key findings

- The application claims Remdesivir, and particularly a diastereomer, which is different from the one disclosed in WO2012012776.
- The D diastereomer claimed in the current case possesses activity against Ebola virus.
- Compounds claimed in this case lack novelty, are inherently anticipated and obvious to try.
- Opposition proceedings are ongoing in India and Argentina.

WO2017049060

Around 32 compounds synthesized, and a method of treating SARS, MERs and coronavirus is generally claimed. Very few compounds are assayed for activity, while Markush covers thousands of compounds. Remdesivir is disclosed, but its evaluation of activity is limited to corona viruses.

Coverage of patent in terms of claims is similar to WO2012012776.

Refer para 0405- Compounds 1, 9 (remdesivir) and 32 tested against Lassa and Junin viruses, (arena viruses) detailed test protocol is provided. The results of three compounds is tabulated, amongst those three compounds, activity of compound 1 was largely not determined. Compounds 9 (remdesivir) and 32 were studied for anti SARS and MERS activity (Corona viruses) and found to be active.

Further testing of compounds 1 and 32 for efficacy and toxicity was continued and also anti-viral activity in monkeys studied for compound 32. The symptoms were less pronounced in compound 32-treated monkeys, and viral RNA in the respiratory tract was significantly reduced in Compound 32-treated animals, refer para 0435, while para 0436 states virus was detected in nose swabs and throat swabs at Day 1, 3, 5 and 6 post-infection There was no difference in viral load between vehicle-treated and Compound 32-treated animals.

Claims 1-38 cover a method of treating Arenaviridae viruses (Junin and Lassa viruses), claims 39-74 are for a method of treating Coronaviridae viruses (MERS, SARS and few more) and claims to use of compounds to make a medicament for treating viruses, a compound to treat the viruses and a kit comprising dosage units of compounds or their stereoisomers, salt, ester, hydrate, solvate, mixture of stereoisomers or tautomers are covered.

Claims 25 and 61 particularly claim the enantiomers (i.e., four different substituents (groups attached)) with P being chiral.

Summary of Observations

- Both (WO2012012776 and WO2017049060) are method of use/treatment patents with very limited data to demonstrate activity against various viruses claimed.
- Compositions, various forms of the compound, kit with dosage forms, combination of drugs (with interferons and favipiravir) and Swiss-type claims are included in the claim set.
- Synthesis and characterization of remdesivir is provided.

Key Findings

1. The coverage of the method claims is far broader than the disclosure.
2. Very poor enablement and disclosure of preferred embodiments.
3. On data for just three compounds, the use claim is extended over the entire Markush.
4. After having claimed activity over one group of viruses in WO2009132135 patent, the following patents just attempt to cover more family of viruses against which the compounds are supposed to be active.

Status of national phase applications:

US 10695361- granted in June 2020, no significant update in the file, claiming a compound (Markush) to its salt for a method of treating a Coronaviridae infection in a human, combinations with other therapeutic agents are also disclosed such as anti-inflammatory, a steroid, a mucolytic, a bronchodilator. The infections claimed are SARS, MERS and so on through different dosage forms, including parenteral through various routes.

US1007208- granted in May 2021, no significant update in the file

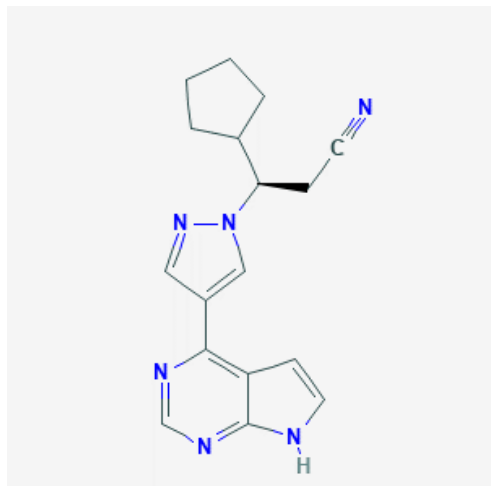
EP3785717- EPO has granted the patent in Dec 2021, EPO has communicated on 24 August 2021 an intention to grant the patent claiming a compound (Markush) to its salt for its use in a method of treating a Coronaviridae infection in a human, combinations with other therapeutic agents are also disclosed such as anti-inflammatory, a steroid, a mucolytic, a bronchodilator. The infections claimed are SARS, MERS and so on through different dosage forms, including parenteral through various routes.

EP3349758- EPO has issued its intent to grant the patent in October 2021, claiming a compound (Markush) to its salt for its use in a method of treating an arenaviridae infection in a human, a narrower Markush and many specific compounds including remdesivir and its diastereomers are claimed, combinations with other therapeutic agents are also disclosed such as anti-inflammatory, a steroid, a mucolytic, a bronchodilator. The infections particularly claimed are Lassa and Junin viruses.

RUXOLITINIB

Background

Ruxolitinib is a drug discovered by Incyte Corporation for the treatment of myelofibrosis. It is covered by a portfolio of around eight patents in over 40 countries.



Molecular formula: C₁₇H₁₈N₆

IUPAC Name

(3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile

Patents Studied

WO2008157208. Filed on 12 June 2008.

WO2007070514. Filed on 12 December 2006.

WO2008157208

With 60 claims, the patent covers three salts of namely maleic acid, phosphoric acid and sulphuric acid salt of ruxolitinib, their process of synthesis, compositions and various methods of modulating JAK and methods of treating various diseases.

The specification has three examples covering the three salts, their synthesis and characterization. An in vitro JAK kinase assay is disclosed and concludes that the phosphoric acid salt and the corresponding free base compound had IC₅₀ values of less than 50 nm for each of JAK1, JAK2 and JAK3. The efficacy of the other two salts is not established.

Claims 7, 8 and 9 cover composition comprising the salts suitable for topical and oral administration.

Claim 10 covers a method of modulating JAK activity and claim 12 covers method of treating diseases associated with JAK activity with compound of formula I. Several diseases are listed in subsequent claims, claim 20 lists a viral disease, and claim 21 states that said viral disease is Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus

(VZV) or Human Papilloma Virus (HPV). Claim 35 lists disease as inflammatory disease and claims 39 and 40 state it is inflammatory disease of upper and lower respiratory tract.

Summary of Observations

- IC50 values for base and one salt provided, that too not exact values.
- No efficacy data for two other salts.
- No test protocols and assay results for the various diseases being treated by the invention is provided.
- Method of treating various viral diseases (but not COVID-19) and inflammation of upper and lower respiratory tract are claimed.
- The three salts are synthesized, characterized and claimed.

Key Findings

1. The salts of Ruxolitinib disclosed in this patent are not novel, due to the implicit disclosure and claim 1 of WO2007070514. Page 35 of WO2007070514 patent covers salts and Ruxolitinib is disclosed as compound of example 67. Refer to page 14 of the Guidelines.
2. Maleic, phosphoric and sulphuric acids are well known acids to synthesize pharmaceutically acceptable salts, literature support for same can be provided. Refer to page 32 of the Guidelines.
3. No enhanced efficacy of salts can be established since WO2007070514 does not provide details.
4. No other property is demonstrated in the patent specification to show that the salts provide a distinct advantage over the base, making the salts highly obvious. Refer to page 14 and 32 of the Guidelines.
5. It is surprising that the ISA for this case made the following observation, see box below and opined all claims to be novel and inventive.

Re Item VI.

D3: WO 2007/070514 A (INCYTE CORP [US]; RODGERS JAMES D [US]; SHEPARD STACEY [US]; MADUSKUIE) 21 June 2007 (2007-06-21)

will not be considered at this stage, since it is not prepublished to the priority date of the present application and it is assumed that the priority has been validly claimed. However, it is noted that claims 1 of D3 encompasses the salts of the present application but there appears to be no specifically mentioned compound in D3 which falls under the scope of the subject matter as presently claimed.

WO2007070514

WO2007070514 has 88 claims. The claim 1 is a Markush structure with options that could conservatively cover thousands of compounds (could run into many more). The description of the options for the Markush covers over four pages and enumerates the multiple options for substituents at every position of the compound i.e., the compound of formula I. The claim also covers pharmaceutically acceptable salts and prodrugs thereof. Claim 45 and particularly claim 46 disclose ruxolitinib (refer page 283 of WO2007070514).

To enable the Markush, over 700 compounds are synthesized and characterized with proton NMR data included in the examples. The examples elaborately cover the various options of the Markush enlisted in claim 1. However, limitation to the broad coverage sought can be made, since some substituents and options are not exercised in any compound.

The example 67 (refer to page 91-92 of WO2007070514) particularly discloses ruxolitinib, its synthesis and characterization. Both R and S enantiomers are disclosed and enabled. Claim 46 particularly claims ruxolitinib (refer page 283 of WO2007070514).

Claims 47 and 48 cover composition comprising compound of formula I suitable for topical administration.

Claim 49 covers method of modulating JAK activity and claim 55 covers method of treating diseases associated with JAK activity with compound of formula I. Several diseases are listed in subsequent claims, claim 63 lists a viral disease, and claim 64 states that said viral disease is Epstein Barr virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-zoster virus (VZV) or Human Papilloma Virus (HPV). Claim 78 lists disease as inflammatory disease and claims 81 and 82 state it is inflammatory disease of upper and lower respiratory tract.

Example A on page 268 of Annexure 1 provides the in vitro assay for JAK kinase, Example B lists cellular assays on the same page as above, Example C: *In vivo* anti-tumor efficacy and Example D: Murine Skin Contact Delayed Hypersensitivity Response Test on page 270 and Example E : *In vivo* anti-inflammatory activity on page 271 list detailed protocols for testing with criteria for evaluating the compounds, but in the entire specification the results of such tests are not provided. So, the activity of the compounds for the claims 49 onwards is not provided or supported in the specification

Summary of Observations

- Large number of examples are provided to support the Markush. They are synthesized and characterized. Partial satisfaction of the Guidelines advice of page 23 is accomplished.
- The preferred compound i.e., ruxolitinib is disclosed, synthesized, characterized and claimed.
- The results of the various assays enlisted to prove the efficacy of the compounds is not disclosed.
- Method of treating various viral diseases (but not COVID-19) and inflammation of upper and lower respiratory tract are claimed.

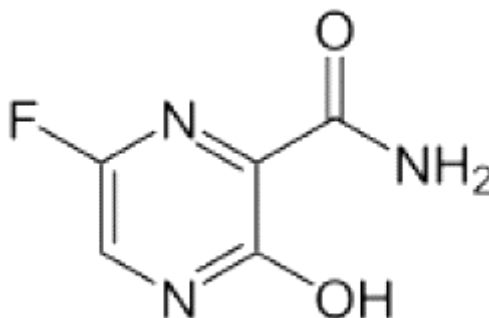
Key Finding

1. The compounds are disclosed and synthesized, but their utility or industrial application is not disclosed. Contravenes advice on page 17 of the Guidelines.

FAVIPIRAVIR

Background

Favipiravir is anti-viral drug developed and manufactured by Toyama Chemical (Fujifilm Group) and was approved for medical use to treat influenza in Japan in 2014. The drug became a generic in 2019, though follow-on patents are still in force.



Molecular formula: $C_5H_4FN_3O_2$

IUPAC name: 6-fluoro-3-oxo-3,4-dihydropyrazine-2-carboxamide.

Patents Studied

1. WO200010569. Filed on 18 August 1999.
2. WO2010104170. Filed on 12 March 2010.

WO0010569

The twenty year term of protection for patents stemming from WO0010569 and counted from its filing date has expired on 18 August 2019.

WO2010104170

WO2010104170 (its equivalent US 8513261 was referred for valid English translated document) with 18 claims covers a tablet and a granulated powder of favipiravir.

The WO0010569 patent states that “The nitrogen-containing heterocyclic carboxamide derivative represented by the general formula [1] of the present invention or a salt thereof can be used as a solution, a suspending agent, a powder, Pharmaceutical preparations such as granules, fine granules, tablets, capsules, syrups, elixirs, alcoholic beverages, lozenges, gargles and aerosols, orally and parenterally (injection, dermal, rectal) In the nasal cavity”, refer column 10, line 51, WO2010104170.

And the WO2010104170 claims a tablet and a granulated powder. The tablet is a conventional tablet prepared by conventional methodologies and contains around 200 mg of compound of formula A, which is favipiravir. The tablet does not overcome any specific challenges other than those posed by conventional tablet formulation development. The ingredients used and claimed in the tablet and granulated powder are known for several years before the filing date of the WO2010104170 patent and known specifically for the functions they are used in the patented formulations

Summary of Observations

- The tablet and granules are anticipated in the WO0010569 patent, but are not explicitly described with the other ingredients as stated by the EPO examiner (refer to the English translation of the ISR and IPRP).
- The disclosure in the patent is a routine experimentation carried out while developing a tablet formulation, and has no non-obvious features.
- The tablet formulation complies to the usually laid down parameters such as hardness and dissolution, and does not seem to overcome any novel challenges or unresolved problems in the art.
- Regarding the drug being 50-95% weight of tablet that is fairly common in many tablets.
- The reply provided by Applicant to EPO (against the citations in the ISR) lists the challenges in formulating a tablet, which are very well known in the art (refer para 2, page 2). The subsequent paras defend the invention in light of the citations, but there are very elementary text book level prior arts that describe the experiments listed in Tables 1 and 2 of the patent WO2010104170.

A standard text book used in graduation studies in pharmacy practice, lists the ingredients used, the techniques employed and the parameters tested.⁴ A 200 mg dose is also very common in pharma formulation and does not pose any unique challenge. In fact, there are drugs with much higher doses in the market (e.g., paracetamol 500 mg).

Key Finding

1. Since there is no single prior art listing a tablet formulation of favipiravir with hydroxyl propyl cellulose and a binder, the claims may be opined novel, (also refer to comments above), however, the invention is highly obvious. Refer to the advice on page 36 of the Guidelines.

⁴ Lachman, L., Lieberman, H., & Kanig, J. *The Theory And Practice of Industrial Pharmacy*, 3rd ed. (Philadelphia: Lea & Febiger, 1986).

TOCILIZUMAB

Background

Tocilizumab is a recombinant humanized monoclonal antibody of the Immunoglobulin G1 (IgG1) class, which is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor.

Tocilizumab is recommended for the treatment of severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and life-threatening cytokine release syndrome induced by chimeric antigen receptor T-cell therapy.

It was developed by Hoffmann-La Roche and Chugai and has been extensively patented in more than fifteen countries with a portfolio of over five patents.

Patents Studied

1. WO199611020. Filed on 7 June 1995.
2. WO2002080969. Filed on 2 April 2002.
3. WO2003068260. Filed on 14 February 2003.
4. WO2004096273. Filed on 28 April 2004.
5. WO2005061000. Filed on 17 December 2004.
6. WO2009084659. Filed on 26 December 2008.

Note

- The original applications have mostly been filed in Japanese, the corresponding US applications therefore have been used for the study.
- The Applicant Chugai has patented this monoclonal antibody, its formulations and various uses extensively and across several countries. Most of the six cases have very long prosecution history with the national patent offices.
- Many of the antibody related or methods related patent specifications contain common text matter, specifically with reference to making of the antibody and its details and characteristics and references.
- The Applicant has attempted to build a substantial portfolio around this antibody.

WO199611020

WO199611020 is expired, no national phase entry later than 1995 seen, so the said application has expired in all countries that it entered in national phase.

WO2002080969

WO2002080969 is an application containing 26 claims pertaining to a therapeutic agent for the treatment of chronic arthritis disease of childhood, where the therapeutic agent is an IL-6 antagonist.

This patent application suffers from various drawbacks:

- Lack of disclosure of what is the IL-6 antagonist. While the dependent claim specifically states that the antagonist is a monoclonal antibody, the specific features and aspects of the antibody is not described.
- Examples pertaining to preparation of antibody is disclosed, but specific features of the antibody which will make it act as the IL-6 antagonist are not disclosed.
- The Complementary determining regions (CDRs) and the specific antigen-antibody binding data is not provided. (Another assay protocol is provided to prove the antigen-antibody interaction, but Complementary determining region or CDR data has been requested by Patent Offices).
- To prove activity against chronic arthritis disease of childhood, one example of one 5-year-old male child treated for juvenile rheumatoid arthritis and one example of a 22-year-old female treated for Still's disease (claimed) is shown in the patent specification.
- The patent cannot be worked without undue experimentation and does not provide adequate written description.
- The US application 2004115197 has been abandoned for failure to respond to queries from Patent Office in 2007.
- There are several relevant prior arts indicating use of an IL-6 receptor antagonist for treatment of rheumatoid arthritis and so the invention lacks non-obvious features.
- Therefore, EPO rejected therapeutic agent as well as use (Swiss-type) claims.
- The case was appealed at the EPO by the Applicant and ultimately refused by the Office and the Appeals Board in 2017.

Key Finding

1. The patent is not in force in US and in countries who are members of the EU but may be allowed in some other countries, e.g., Australia. A corresponding application in the Indian Patent Office is not filed.

Status of national phase filings:

There are four EP filings.

EP 3640261 was deemed to withdrawn as on 12 November 2020 due to no response within time limit set to reply to EPO, but late fee and response has been posted on 22 January 2021 and EPO has communicated on 5 February 2021 to allow further processing of the case, There are no further updates. In the response submitted to EPO, Applicant has amended claims to cover the second medical use for the treatment of systemic onset of juvenile rheumatoid arthritis.

The second EPO filing, EP 1374900 has been closed by EPO after an appeal by the Applicant in 2017 and there is no further action, so it is refused and withdrawn. The third EPO filing i.e., EP 2298812 is withdrawn in 2019 and there is no further update in this case. EP 1972638 has been refused in 2017, no further update in this case.

There are five US filings.

US 10/473165 is abandoned since 2007, US 14/986884 was allowed in 2018, but the last update in 2018 is that the case is abandoned, due to non-payment of issue and publication fee.

US 11/704233 is granted as 7,955,598 in 2011, claims a method for treatment of adult-onset Still's disease, comprising administering an antibody against an IL-6 receptor to a patient who needs said treatment, wherein the antibody against the IL-6 receptor is an antibody which inhibits binding of IL-6 to the IL-6 receptor by binding to the IL-6 receptor, and the file has no updates after 2013.

US 13/064953 is granted as 9,255,145 in 2016 claims A method for treatment of systemic-onset type juvenile rheumatoid arthritis, comprising administering an antibody against human IL-6 receptor to a human patient who needs said treatment, wherein the antibody against the IL-6 receptor is an antibody which inhibits binding of IL-6 to the IL-6 receptor by binding to the IL-6 receptor, and there are no updates in the file after 2016.

US 15/946866 is under prosecution.

WO2003068260

WO2003068260 discloses a composition of an antibody to IL-6R (Interleukin-6 receptor).

The claim 1 of this application is as broad as: An antibody-containing solution formulation including a sugar as a stabilizer. The claim may include any antibody and such a claim does not even enjoy novelty and is completely unsupported by the specification for all the possible antibodies that could be covered by such a claim. Claim 14 however states that the antibody is an anti-IL-6 receptor antibody.

The patent also claims a method of stabilizing the formulation and method of inhibiting formation of multimers, which are formed when the formulation is subjected to freeze-thaw cycles.

The specific antibody is not adequately disclosed in terms of CDRs and other specific characterization data.

The excipients used are a sugar and a surfactant, which are very well-established ingredients in a pharmaceutical formulation. They are well known to stabilize antibody formulations also. The patent specification provides extensive studies with respect to interaction between the antibody and the excipients, establishing the best suited ones for the formulation. These are routine studies in formulation development of trial and error and is part of optimization of the formulation's ingredients. This does not involve an inventive activity, but an extensive exercise to eliminate the excipients that do not provide stability and choose the ones that do. Formulations have to be stable throughout the shelf-life or till expiry and is a regulatory requirement. The sugars and the surfactants that have been employed here are very well-known ingredients in the art, and have been widely used in formulation development.

The case has been allowed in US with the main claim being: refer US 8840884

1. A stable solution pharmaceutical formulation comprising a humanized anti-interleukin-6 receptor IgG1 antibody in an amount from 17.5 to 22.5 mg/ml, sucrose in an amount from 25 to 100 mg/ml, surfactant as a stabilizer, and phosphate buffer, wherein the pH

of the formulation is from 6.5 to 7.0, wherein the sucrose inhibits dimerization of the antibody; and

2. Sixth claims is: A freeze/thaw stable solution pharmaceutical formulation comprising humanized anti-interleukin-6 receptor IgG1 antibody in an amount from 17.5 to 22.5 mg/ml, sucrose in an amount from 25 to 100 mg/ml, surfactant as a stabilizers, and sodium phosphate buffer, wherein the pH of the formulation is about 6.5, wherein the sucrose inhibits dimerization of the antibody.

Two more narrow claims of the formulation with specific quantities of sucrose and polysorbate (surfactant) and antibody has been allowed with specific pH (i.e., no ranges).

The patent family to which this patent application belongs is extensive, with grants in many countries and several divisionals and family members covering both a) varied formulations as well as b) method of stabilizing or inhibiting formation of impurities/dimers and so on. However, all have essentially the same ingredients i.e., a sugar and a surfactant and all are highly obvious. Narrowest embodiments are claimed and protected through the various granted patents.

The International Search Report opined that the claims lacked novelty and inventive step citing 17 documents, but eventually there are two US and three EP grants.

Key Findings

1. The formulation with a sugar (specifically sucrose) and surfactant is protected, though highly obvious. The claims are narrow and it may be possible to work around the claimed invention.
2. The family is very large and all members are covering various narrow aspects of stabilizing the formulation, though essentially using a sugar and a surfactant.

Status of national phase filings:

EPO: EP 2311489 was refused and the file is closed by EPO. EP 3578168 is under examination for a third generation divisional filed (three are filed) in 2019 claiming priority of the 2003 application. The current claim is to a method of inhibiting the formation of antibody multimer molecules. The earlier claimed sugar i.e., specifically, sucrose and surfactant are covered and the antibody is specified to be anti-IL-6 antibody hpm-1. The amended claims as listed above were filed after the EPO opined that only such claims are novel, though not inventive. EP 3192528 has been withdrawn by 2019, and no further updates in the file.

USPTO: US 8840884 is granted. Claims a stable solution of the antibody with sucrose, a surfactant, and a phosphate buffer, and also claims the inhibition of dimerization of the antibody by the stable solution when it is subjected to a freeze/thaw cycle. A second granted patent is US 9051384, divisional of US 8840884. US 9051384 claims a method of stabilizing the antibody solution of the US 8840884 patent combining the ingredients claimed therein.

WO2004096273

The English translation filed at the Indian Patent Office has been used for reference.

The application was filed with 80 claims pertaining to a pharmaceutical composition, use claims and method claims.

The main claim reads as:

A pharmaceutical composition for the treatment of IL-6 related diseases, comprising an interleukin 6 antagonist (IL-6 antagonist) and immunosuppressants.

Another claim reads as: “A therapeutic agent for the administration at high doses, comprising an IL-6 antagonist”.

Another independent claim reads as:

A use of an interleukin-6 antagonist (IL-6 antagonist) and immunosuppressants for the production of a pharmaceutical composition for the treatment of IL-6 related diseases.

A fourth type of claim reads as:

A method for the effect enhancement on the use of an IL-6 antagonist for the treatment of IL-6 related diseases, comprising administering immunosuppressants and an IL-6 antagonist to a patient requiring such a treatment.

The claims as filed are very broad, vague, indefinite and their metes and bounds are completely undefined.

The terms IL-6 related diseases, interleukin 6 antagonist (IL-6 antagonist) and immunosuppressants, administration at high doses and pharmaceutical composition for the treatment of IL-6 related diseases are all very broad, indefinite terms. IL-6 diseases can be any disease that involves interleukins in any manner and can be a huge list of possible diseases that can fall under the term IL-6 diseases and the patent specification has not provided adequate data or covered all these various possibilities. Similarly, IL-6 antagonist and immunosuppressant can mean a large number of possible candidates and this needs to be specified.

Thus, the IL-6 diseases, the IL-6 antagonist and the immunosuppressant are to be defined in claim 1 to overcome the above-mentioned objections.

Further, such claims as listed above lack novelty. There are several documents that will qualify as prior arts for such claims.

Also, even if the claim are made definite by specifying the IL-6 disease as rheumatoid arthritis, IL-6 antagonist as a monoclonal antibody and immune suppressant as Methotrexate, the composition should specify the concentrations of all the ingredients. Even then such compositions are generally covered in prior arts, though specific concentrations may not be disclosed or claimed in prior arts.

The huge amount of literature that can affect the novelty of the invention is evidenced by the citation of at least eight documents in the International Search Report and in the various Office Actions issued by the various national patent offices.

Further, the method claims are not patentable in some domains. e.g., EPO, India, and use claims are not allowed in some domains. Thus, the composition claims with amendments to make them definite have been pursued in EU (with use claims) and method claims have been pursued in US.

The status of the application in India is not updated, but appears to be abandoned, out of three EP filings, one was refused and oral proceedings has been withdrawn, second one has been withdrawn and in a third one with a narrow claim with dose of IL-6 antagonist specified in combination with Methotrexate is being pursued with an oral proceeding summoned.

USPTO has granted two narrow method claim patents.

Key Findings

1. The claims are too broad and indefinite.
2. As filed claims are not novel.
3. All cases have long prosecution history.
4. Compared to the as filed claims, the few grants have a narrower scope and few are method claims only.

Status of national phase fillings:

Status in the US:

Granted as US 7521052 in 2009 with a single claim which reads as: A method for treating rheumatoid arthritis, comprising administering an effective amount of an anti-IL-6 receptor antibody (anti-IL-6R antibody) and an effective amount of methotrexate (MTX) to a patient in need thereof, wherein the anti-IL-6R antibody is a humanized PM-1 antibody. This had six fillings at USPTO as child patents, of which two were abandoned, two are pending and two are granted. A challenge to the granted claim 1 has been filed recently, i.e., on 6 January 2022 citing two documents to be affecting novelty of granted claim 1 and one document to be affecting non-obviousness of claim 1. Grounds for opposing also include reasons as to why claim 1 is objected to because it does not specify whether the antibody and MTX are being administered simultaneously or sequentially, and that the claim 1 seems to encompass both the possibilities.

Of the two granted cases, US 8709409 claims a method for treating rheumatoid arthritis, comprising administering an effective amount of an interleukin-6 (IL-6) antagonist and an effective amount of methotrexate (MTX) to a patient in need thereof, wherein the IL-6 antagonist is an anti-IL-6 antibody which inhibits binding of IL-6 to the IL-6 receptor by binding IL-6 and blocks signal transduction by IL-6. This case was issued in April 2014 and there are no further updates on the file.

The second case is US 10744201 granted in 2020 claims a method for increasing the likelihood of achieving an American College of Rheumatology (ACR) 70 response in a rheumatoid arthritis patient compared to treating the patient with methotrexate (MTX) alone, comprising administering to the patient a combination of (i) 8 mg/kg of a humanized anti-interleukin-6 receptor (anti-IL-6R) antibody MRA every four weeks, wherein the anti-IL-6R monoclonal antibody MRA is administered intravenously, and (ii) MTX orally administered once per week at a dose in a range of 10 to 25 mg. Recently on 06 January 2022, a challenge to the granted patent has been filed citing two prior arts rendering the claims anticipated and obvious.

Status in EPO:

The EPO applications claim the priority of the 2004 Chugai filing for tocilizumab as listed above. EP 3167901 is a first generation divisional and is in appeal after EPO rejected the application.

EP 1617869 has been withdrawn and the file is closed since 2016.

EP 3903819 is a second generation divisional undergoing prosecution for claiming the use of and anti-IL-6 receptor antagonist antibody with methotrexate in the treatment of rheumatoid arthritis. The EPO has cited one document opining the claims to be obvious, also citing the appeal in process for the '901 case.

EP 2368577 was refused by EPO and appealed, but was withdrawn in April 2020 and refused in July 2020, no further updates.

WO2005061000

This patent pertains to an agent to prevent vasculitis, which is an IL-6R antibody. The patent specification (as in other applications by Chugai, except where stability of formulations is claimed) lacks disclosure with regard to antibody's features, CDRs, sequences and binding affinity.

The patent cannot be practiced without undue experimentation, since the claims include a preventive and/or a therapeutic agent for vasculitis, the use of interleukin-6 (IL-6) antagonist for the manufacture of a preventive and/or therapeutic agent for vasculitis (Swiss claim) and a method of preventing and/or treating vasculitis comprising administering an interleukin-6 (IL-6) antagonist to a subject in need thereof. To support the agent's activity in vasculitis, two patients were studied, one a 19-year-old female and second a 42-year-old male and activity and method are concluded on this basis.

The case has been filed in many countries, granted in a few, refused in a few, and there are no updates in a few. In US method claims are granted in 8617550. (use and agent claims -not allowed) There appears to be no divisional application. This case was filed in India, 3057/DELNP/2006, and was objected in the Examination report for following reasons: Method and use claims-not patentable under Sec 3(i) and new use under Sec 3(d) and agent claims being obvious in view of cited prior arts. The reply to the Examination report has not been filed within time limits, (deemed to be abandoned) but there is no update on the status of the case.

EPO had granted this patent for agent and use claims, EP1707215. Further, the EPO granted patent has been withdrawn on 13 February 2020, since the patent was revoked. The patent was objected on the grounds of lack of novelty and inventive step and insufficiency of disclosure. From the two patients treated and exemplified in the patent specification, it is difficult to conclude that the agent claimed therein can treat any type of vasculitis as claimed.

Key Findings

1. Only method claims are allowed in US.
2. Therapeutic/preventive agent for vasculitis is a rejected claim in US.
3. The patent stands revoked in EPO.

Status of patent fillings:

Status in US:

US 8617550 granted in 2013 covers a method of treating vasculitis comprising administering an antibody against IL-6 receptor to a subject in need thereof, no update in file after 2017. This case had an additional family member in US, but was abandoned in 2015.

Status in EPO:

EP 1707215 was granted in 2012 with the principal claim being an agent for use in preventing and/or treating vasculitis the agent being an antibody against IL-6 receptor, wherein the antibody inhibits the binding of IL-6 to the IL-6 receptor. This patent was opposed and eventually revoked in 2020.

WO2009084659

The patent claims are very broad stating a stable antibody-containing liquid formulation, characterized by comprising arginine and methionine (from translated document submitted to Indian Patent Office). 20 claims are on file, while US application contained only two claims. Another independent claim on this file is a method of inhibiting deamidation of molecules of an antibody in a liquid formulation containing the antibody, comprising adding arginine to the liquid formulation.

One of the most relevant prior arts is Chugai's earlier filing, refer WO 200213860, wherein the histidine buffer and use of surfactant as stabilizer as well as addition of arginine is claimed. There are more prior art documents, making the invention highly obvious.

Status of national phase fillings:

Status in US:

US 8568720 granted in 2013 and there are no subsequent significant updates in the file thereafter. It was filed with 20 claims and allowed with two claims claiming a stable liquid formulation suitable for subcutaneous administration comprising 180 mg/mL humanized anti-IL-6 receptor IgG1 antibody, 100 mM arginine, 10 to 50 mM methionine, further comprising 0.005 to 3% polysorbate 80 and 20 mM histidine buffer, said formulation having a pH of 6. The second claims stated that the antibody comprises the humanized anti-IL-6 receptor IgG1 antibody MRA.

US 20140005367 and US 20160090419 were abandoned in 2016 and 2019 respectively and there are no further updates in this file.

US 20200079857 is granted as US 11008394 in May 2021 with 16 claims wherein claims 1, and 7 claims methods to inhibit deamidation of the antibody using arginine and histidine buffer, the method of claim 7 additionally comprising adding polysorbate 80. Further independent claims 11 and 14 are similar to 1 and 7 respectively except they additionally cover the "wherein the arginine inhibits dimerization or deamidation of the antibody in the formulation."

US20210246216 is under prosecution, last activity is responding to USPTO in Feb 2022. The application claims a stable concentrated liquid antibody formulation suitable for subcutaneous administration, comprising: 150 to 200 mg/mL of a humanized anti-IL-6 receptor antibody MRA; 50 to 300 mM arginine; and histidine buffer, pH 6.0 and a method to inhibit deamidation or dimerization of the formulation.

Status in EPO:

US 8568720 and EP2238985 are granted with a single example as allowed claims.

The EP2238985 and IN respective patent were granted with far broader scope of claims. Glaxo opposed in EPO and after a prolonged proceeding, upheld claiming a stable antibody-containing liquid formulation comprising 180mg/ml of the humanized anti IL-6 receptor antibody MRA, 100 mM arginine and 30 mM methionine, 0.5mg/ml polysorbate-80, 20mM histidine buffer solution and having a pH 6.0. Further a method of preventing dimerization of antibody in a liquid formulation by adding methionine and arginine is claimed.

While in IN there was no opposition.

In the US the prosecution was very long. The allowed claims are listed herein:

1. A stable liquid formulation suitable for subcutaneous administration comprising 180 mg/mL humanized anti-IL-6 receptor IgG1 antibody, 100 mM arginine, 10 to 50 mM methionine, further comprising 0.005 to 3% polysorbate 80 and 20 mM histidine buffer, said formulation having a pH of 6.
2. The stable liquid formulation of claim 1 wherein the antibody comprises the humanized anti-IL-6 receptor IgG1 antibody MRA.

Granted claim 1 covers a particular concentration of the antibody and with a particular buffer and arginine concentration. So, in terms of coverage or scope, the claims are very limited and narrow.

Key Findings

1. Scope of patent very narrow.
2. Few embodiments lacked novelty and were highly obvious.
3. They pertained to formulations with obvious pharmaceutically acceptable excipients with obvious effects.
4. The patent was opposed in EPO and scope of claims restricted.

SILTUXIMAB

Background

Siltuximab is a chimeric (made from mouse and human proteins) monoclonal antibody patented by Centocor Inc. Siltuximab targets the IL-6 receptor (Interleukin) and inhibits its activity. It has been investigated for activity against many cancers, but is approved by FDA for the treatment of patients with idiopathic multicentric Castleman's disease (iMCD), who do not have human immunodeficiency virus (HIV) or human herpesvirus-8 (HHV-8). The antibody has been patented in over 15 countries globally, in addition to a few European countries.

Patent Studied

1. WO2004039826. Filed on 26.10.2002

WO2004039826

The WO application discloses at least one novel chimeric, humanized or CDR-grafted anti-IL-6 antibodies derived from the murine CLB-8 antibody, including isolated nucleic acids that encode at least one such anti-IL-6 antibody, vectors, host cells, transgenic animals or plants, methods of making and using thereof, including therapeutic compositions, methods and devices.

A murine IL-6 monoclonal antibody (referred to as CLB-8) is known with high affinity to IL-6 receptor, however its complementary directing regions or antigen binding regions are not known. Murine antibodies are immunogenic in humans and decrease their therapeutic value. Thus, for an improved pharmaceutical profile and increased affinity, a new monoclonal antibody was required, which is the chimeric siltuximab.

The WO application claims multiple inventions, there are nearly 15 inventions covered in this application:

The monoclonal antibody, an isolated antibody coding nucleic acid, an antibody vector, a host cell comprising the nucleic acid, a method of producing the antibody, an IL-6 antibody composition, a method of treating an immune disorder, a method of modulating a cancerous disorder, a medical device comprising the IL-6 antibody, a formulation comprising the antibody, a method of preparing the formulation, a method of treatment, an article of manufacture and a transgenic animal or plant expressing the antibody.

The claims pertaining to the antibody i.e., claims 1-9 are supported in the description and through the examples. The antibody encoding nucleic acid, the antibody vector and a host cell comprising the nucleic acid are also described in the WO specification.

The antibody and its method of manufacture is described and exemplified in the WO specification, however, the other inventions particularly, the pharmaceutical compositions and formulations are not disclosed by way of even a single example. Same applies to the claim on the medical device and for the huge number of diseases against which the antibody is expected to possess activity. The claims pertaining to compositions, formulations and device cannot be worked without undue experimentation.

There is no evidence in the patent specification that the antibody indeed exerts its effect against the huge number of disease and disorders listed and claimed, refer claims 23-26, especially claim 26.

Referring to claim 35, a very long list of agents that are to be administered with or after administering the antibody, the specification has no examples of such compositions or the effect of such combinations and their effects. Referring to page 61 of the specification where agents co-administered are listed, anti-viral agents is listed and so is hydroxychloroquine sulphate.

Claims 54-58 claims a transgenic animal or plant for producing the antibody and expressing the antibody is claimed.

Summary of Observations

- Multiple inventions are covered in a single patent application, so at national phase there may be several divisional patents to be watched for.
- The claim to the antibody appear to be novel and inventive.
- Claims to compositions, methods of use, treatment and formulations, combinations and device are poorly supported and not enabled.
- The list of diseases that can be potentially treated and the list of agents that the antibody can be combined with seem too long, with no specific supporting data to back such claims.

Key Finding

1. While the main claim to the anti-IL-6 receptor chimeric antibody is supported and is novel and inventive, the other inventions are not enabled in the patent specification and the claims are too broad and unsupported.

SARILUMAB

Background

Sarilumab is a fully human monoclonal antibody patented by Regeneron Pharmaceuticals for the treatment of rheumatoid arthritis that targets the IL-6 receptor (Interleukin). The antibody has been patented in over 15 countries globally, in addition to a few European countries.

Patents Studied

1. WO2007143168. Filed on 1 June 2007.
2. WO2011085185. Filed on 7 January 2011.

WO2007143168

The WO2007143168 patent has claimed very broadly for an antibody or an antigen binding fragment that binds to IL-6receptor. The claims of the WO patent i.e., claim 1 as such has not been granted in the US, India or Europe. The as filed WO patent lacks support in the written description and enablement for the broad claim 1. The claim refers to an antibody or antigen-binding fragment, which specifically binds to human interleukin-6 receptor (hIL-6R) with a K_D of about 500 pM or less and 300 pM or less, measured by plasmon resonance. K_D refers to the affinity of the antibody to the receptor.

Essentially, the claim 1 could refer to any antibody or antigen-binding fragment that possesses the specified K_D values, with no other characteristics defined. This could lead to a huge number of possibilities and therefore this claim is not even searchable. For e.g., Tocilizumab is also an antibody that binds to hIL-6R with K_D less than 600 pM, and the first patent filing of Tocilizumab or FR 2694767 would be a novelty destroying prior art for the WO2007143168 patent.

The antibody Sarilumab contains two heavy chains and two light chains of polypeptides linked by disulphide bonds. Each heavy and light chains have a variable and a constant region. The light chain comprises one domain and the heavy chain constant region comprises three domains. The variable region in the heavy and light chains are subdivided into regions of hyper variability known as complementary determining regions (CDR) interspersed with more conservative regions known as framework regions. Each variable heavy and light chains is composed of three CDRs and four framework regions arranged from amino terminus to carboxy terminus arranged in the order, FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

The antigen binding capacity of the antibody depends on all the three CDRs on each of the light and heavy chains and defining merely one of them on each of the heavy and light chains will not aid the person skilled in the art to arrive at the antibody with the affinity claimed. In antigen-antibody interaction, it is well known that it is the interplay of the six specific CDRs to obtain the claimed affinity and specificity. Since this is not defined in clams 1 and 2 of the filed WO claims they are opined not inventive. The other claims are still not adequately specifying the requisite six CDRs, however claim 7 claims the antibody with the required six CDRs, though all pairs are not enabled enough in the patent specification.

The other claims cover a nucleotide coding for the antibody, a host for the nucleotide, a host-vector system, a method producing antibody, uses of the antibody a pharmaceutical composition comprising the antibody.

Paragraphs 0016 and 0042 of the specification disclose a pharmaceutical composition comprising the antibody with a pharmaceutically acceptable carrier. But an injection is not covered.

Summary of Observations

- Large number of CDRs are claimed, but not supported in the specification.
- Only few CDRs are well supported in the description and only those particular three heavy and three light chain CDRs can give the required K_D .
- Pharmaceutical compositions are broadly described and claimed.
- Use of the antibody for several IL-6 mediated diseases are claimed, including inflammatory diseases are described, but viral infections are not covered or claimed.

Key Findings

1. The FR 2694767 patent can be a novelty destroying prior art for claim 1 of the WO2007143168.
2. The EPO granted patent has the broadest claim coverage, while the corresponding US and IN patents are narrower specifying the CDRs of the heavy and light chains in claim 1, of specifically embodied CDRs only.
3. The scope of claims 1 and 2 of the WO patent application is too broad and lacks support in detailed description and examples and is not workable without undue experimentation.
4. The granted US and IN claims are enabled, supported and described and are novel and inventive.

Status of national phase applications:

20 National phase applications filed including in EPO (3 filings), China, Japan and India and granted in most countries. Patent family indicates filings in few more countries. No recent events is listed in this file. In two EPO filings the case is granted, and period for opposition has expired. The status of the third EPO case, EP 2012191147 is indicated as withdrawn in the WO site, but the EPO site provides no further details.

The provisional patent applications in US 60/810664 and US 60/843232 have been allowed to expire. In US, the application has matured into several granted and in-prosecution patents.

The various patent applications filed and their status are as follows:

1. US 7582298 granted in 2009 has been issued a patent term extension of 1451 days on 14 January 2021 for the marketed product Kevzara. So, the extension is from 1 June 2027 for 1451 days, i.e., to 22 May 2031
2. US 8043617 granted on 2011-No significant updates in the file
3. US 8080248 granted in Dec 2011-No significant update in the file
4. US 8183014 granted in 2012- No significant update in the file
5. US 8192741 also granted in 2012- No significant update in the file
6. US 20130157313 which was abandoned in 2014
7. US 8568721 granted in 2013-In 2020 there has been correspondence wherein the Applicant has accepted the patent term extension provided to item 1 i.e., US 7582298 and not to US 8568721, i.e., item 7.

8. US 9308256 granted in 2016-No significant update in the file
9. US 20140255995 was abandoned in 2016
10. US 9884916 granted in 2018- No significant update in the file
11. US 10584173 granted in 2020- No significant update in the file
12. US 20210009698-undergoing prosecution, Applicant has to reply to an election restriction OA

WO2011085158

This application claims formulation of Sarilumab with a sugar, an amino acid and optionally a non-ionic surfactant as pharmaceutically acceptable carriers.

A formulation is anticipated in the WO2007143168 patent, but not particularly an injectable. The novelty of the claims lie in the new antibody. The carriers employed are those well known in the art, even before the WO2007143168 patent.

The WO2011085158 claims a pharmaceutical formulation comprising:

- i) A human antibody that specifically binds to hIL-6R
- ii) Histidine and
- iii) A carbohydrate

The carbohydrate is claimed to be Sucrose.

The formulation may optionally comprise a nonionic surfactant selected from polysorbate 20, polysorbate 80 or polyoxyethylene sorbitan monooleate.

Further Arginine is also claimed to be added to the formulation, refer claim 15.

The ingredients are very common for use in formulating antibodies to be delivered as an injection.

The use of a sugar, particularly sucrose and Histidine as a buffer to stabilize the formulation and decrease freeze-thaw is very well established before the filing date of this application. Addition of Arginine is known to further stabilize the antibody injectable formulations.

Literature exists to establish the excipients to be added to antibody formulations and the inventors have used very well established and well-known ingredients. They have standardized the ranges of their concentrations, but that is routine experimentation in formulation development.

The ingredients are known to impart stability to the antibody formulations, and exactly the same is proved in the patent application. Nothing non-obvious there, expected results have been obtained.

That “the stability of sarilumab is a problem in the art” is not stated anywhere in the patent. Stability of formulation is one of its basic criteria and this patent provides a stable formulation using pharmaceutically acceptable ingredients well established in the art.

Summary of Observations

- The formulation uses ingredients well-known in the art as excipients.
- Each of Histidine, Arginine, Sucrose and a non-ionic surfactant are well known through prior arts to be used for stabilizing an injectable antibody formulation and this invention claims the same ingredients.

- The Complementary determining regions claimed in this patent are different from the ones claimed in the WO2007143168 patent.
- The patent covers the use of this formulation for treatment of viral diseases, refer page 17-18. The formulations are useful for treatment, prevention and/or amelioration of any disease or disorder associated with IL-6 receptor. Examples include viral infection, e.g., HIV, EBV infection.

Key Findings

The formulation patent WO2011085158 is highly obvious, with no evidence of inventive activity.

Status of national phase applications:

15 National phase applications filed including in EPO, China, Japan and India and granted in most countries. Patent family indicates filings in more countries, with 39 family members. No recent events listed in this file.

In the EPO, the patent is granted, and period for opposition has expired in 2019 and there is no recent update.

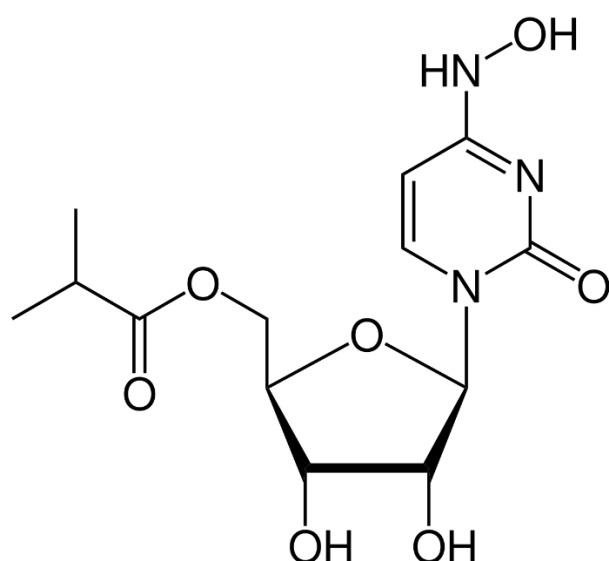
US filing status:

1. US 9173880-granted in 2015-No recent update in the file.
2. US 10072086-granted in 2018-No recent updates in the file.
3. US 11098127-granted in April 2021, no recent updates in the file.
4. US 20210230283-Filed in April 2021, published in July 2021, a continuation application of cases 1-3 as listed above, undergoing pre-exam processing.

EPO filing status:

1. EP 2521536 granted in 2018, period to oppose the patent has expired, no significant updates in the file.
2. EP 3756652 has been filed at EPO in July 2020 and a request for examination has been filed in June 2021, no further update on the file.
3. EP 3409269 is granted in August 2020 and period for filing Opposition has expired in June 2021. No further updates.

MOLNUPIRAVIR



Chemically molnupiravir is the isopropylester prodrug of the ribonucleoside analogue β -D-N⁴-hydroxycytidine (MK-4482, EIDD-1931, or N-hydroxycytidine), 1-(3,4-dihydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-4-(hydroxyamino)pyrimidin-2-one (EIDD-01931) C₁₃H₁₉N₃O₇, Trade name: Lagevrio, assigned to Merck and Co.

On 4/11/2021, U.K.'s Medicines and Healthcare Products Regulatory Agency authorized Molnupiravir for the Treatment of Mild-to-Moderate COVID-19 in Adults with a Positive SARS-CoV-2 Diagnostic Test and Who Have at Least One Risk Factor for Developing Severe Illness, <https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra>.

Emory University has filed for a patent application for this drug, a Markush covering several millions of possibilities and Molnupiravir is one of them. The patent specification has disclosed the synthesis and characterization data for few compounds, around 30 and activity data for few compounds. A number of protocols to be tested against several virus families alone or in combination with other anti-viral agents or agents in other therapeutic classes is described, but not exemplified. The specification lacks sufficiency of disclosure for the huge number of possible compounds as well as for the wide range of activity and combinations it describes and claims.

The PCT: WO2016106050 i.e., PCT/US2015/066144 published on 30 June 2016 claims a pharmaceutical composition of compound of formula I, which is a Markush structure covering millions of possible compounds. Further Claims cover narrower versions of compound of formula I with fewer options and substituents, yet a huge number of possible compounds are in the ambit of the claims i.e., compound of formula Ib, Ic, Id and Ie. There is also a compound of formula II. Further the composition comprises propellants and a pressurized container with compound of formula I is also claimed. Claim 14 onwards method of treating or preventing a viral infection and a large number of viruses are covered.

The International search report has cited two documents that are in X category i.e., affecting the novelty of claims 1-2 and 14-18 and claims 1 and 4 respectively, US 20030087873 and US 20140235566. 6 more documents were cited for affecting the inventive step of most claims 1-22.

In India, four pre grant oppositions have been filed for this national phase application, 201717025098 titled N4 HYDROXYCYTIDINE AND DERIVATIVES AND ANTI VIRAL USES RELATED THERETO. Almost all the oppositions objected to the patent on the grounds of lack of novelty, inventive step, not patentable in view of Sec 3d and 3e. For example, the opposition <https://ipindiaservices.gov.in/PatentSearch/PatentSearch/ViewPDF> gives a very detailed review of why the compound is neither novel nor inventive.

Further proceedings after filing of Opposition before grant by the Indian Patent Office (IPO) is awaited.

An examination report has been issued by the IPO which has been responded to within set time lines along with claim amendments. However, the amendments do not make the claims novel and nonobvious. The objections listed in the documents laying grounds for opposing the patent remain valid for the amended claims also. The filing is awaiting examination after claims have been amended.

Molnupiravir is anticipated in view of WO0232920 and WO2014070771 and lacks any technical advancement in view of the same document. The compound lacks novelty and is obvious to a person skilled in the art. Neither is the therapeutic efficacy enhanced over the two cited prior art, nor does the compound solve any problem associated with the prior art compounds.

The Markush-type claims are very broad with many options of substituents and with a potential to cover millions of compounds. Hence, the requirement of sufficiency of disclosure is not complied with.

The claims also cover a pharmaceutical composition of the compounds and methods of preventing or treating various viral infections. Molnupiravir, EIDD-1931 is exemplified in e.g., 3 for its synthesis and characterization along with a few more compounds (about 30).

Assays: Primary screening for many viruses, Lassa fever virus, ebola, nipah, dengue, SARS coronavirus, influenza, hepatitis, RNA and DNA polymerase, HIV are described, Pharmacokinetics in rodent models is described, also chikungunya in mouse model is studied. The results of several derivatives of EIDD-1931 against the various assays is provided. Molnupiravir and its derivatives are potent anti-viral compounds.

The Medicines Patent Pool (MPP) signed a license agreement with Merck Sharp & Dohme (MSD) for Molnupiravir allowing sublicenses to approved entities in the territory and in form of the sublicense agreement (see <https://medicinespatentpool.org/licence-post/molnupiravir-mol>).

Key findings

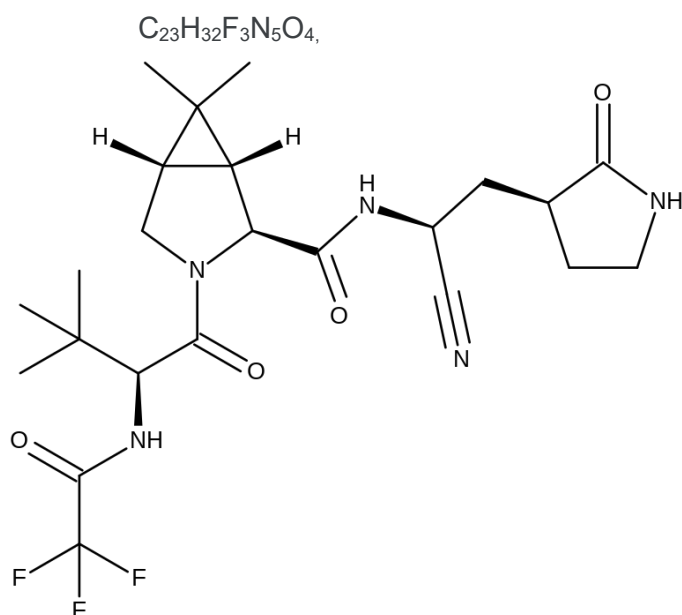
- Main claims are to pharmaceutical compositions for compounds of formula I, Ia, Ib and so on. The Markush covers huge possibility of compounds.
- The number of compounds exemplified and evaluated for anti-viral activity are very few compared to the scope of coverage of the Markush.
- Amongst the options for the pharmaceutical composition, inhaler seems to be the preferred one, with the same claimed.
- The compounds have been evaluated against a wide variety of viruses, the derivatives of molnupiravir are found to be potent.
- The International Search Report as well as Opposition document filed show compounds to be lacking novelty over cited prior arts.

Conclusions

- Even though the exemplified compound of the various Markush formula are potent, they lack novelty and are highly obvious.
- Molnupiravir may be novel, but is highly obvious in light of cited prior arts.
- The derivatives and various compounds assayed are potent anti-viral agents, however their anti-viral activity is anticipated in view of prior arts.
- The application lacks sufficiency of disclosure given the huge number of compounds that is covered by the Markush formulae claimed.

NIRMATRELVIR

Nirmatrelvir (PF-07321332), is (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, published on 16/12/2021 as WO 2021/250648, PCT IB2021/057281 drawing priority from US applications filed by Pfizer Inc between September 2020 and May 2021. The chemical structure is:



The patent covers the following:

Markush structures with a large number of possibilities are described in the patent specification.

Pharmaceutical compositions for oral, inhaled and subcutaneous administrations are covered in combination with remdesivir, dexamethasone or azithromycin amongst various mabs and other COVID-19 repurposed anti-viral agents including molnupiravir.

Coronavirus infections are covered, particularly COVID-19. Nirmatrelvir (E 61) – Crystalline forms, solvates, hydrates and amorphous forms are disclosed and exemplified. Single crystal data, PXRD and physico-chemical data for some compounds are included. Formulation details are also provided in one example.

Anti-viral assay for SARS-CoV-2 has been performed for nearly 100 compounds, their salts, derivatives and various forms (isomers, enantiomers, diastereomers and crystalline forms) and the EC₅₀ values are provided in Table 2. Some compounds seem to be very potent inhibitors of the virus.

Key findings:

- The Markush is broad and can cover a large number of alternatives.
- Nearly 100 compounds are synthesized and characterized including the compounds, their salts, amorphous and crystalline forms and isomers of various types.

- They have all been assayed for SARS COV-2 activity and many are possessing low EC50 values, indicating their potency.
- The specification describes combinations with a large number of possible COVID-19 therapies, but data supporting the combinations' efficacy is not provided.
- Other than Markush, Nirmatrelvir is explicitly described, exemplified, assayed and claimed.
- Methods of treating COVID-19 with the compound and oral co-administration with ritonavir is claimed.
- The International Search Report has cited three documents affecting the inventive step of compounds of claim 1, but specific compounds may be deemed upon examination to be novel and inventive, essentially because of their potent anti-viral activity. There is one document that has been published after the priority date that discloses Nirmatrelvir as a potent anti-viral agent, Chemical Engg News, (2021) 99(19), pages 28-31, Halford Bethany, "To conquer COVID-19, create the perfect pill".

Conclusions

- The broad coverage of the Markush appears obvious for anti-viral activity, however, the specific compounds being novel and potent anti-viral agents may pass the bar for non-obviousness.
- Compounds seem to be potent anti-viral agents.
- The patent discloses, exemplifies, assays and claims nirmatrelvir for treating COVID-19.
- 30 months deadline for entry to national phase falls on 3 March 2023.

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