REGIONAL ACCESS TO MEDICINES DIALOGUE FOR ACTIVISTS IN THE EU
The Second Global Summit on IP and A2M – Virtual Pre-Summit
Doha Declaration@20: Reimagining Access
14 – 21 November 2021

Hosted by the European Alliance for Responsible R&D and Affordable Medicines
Wednesday 17 November, 09:30-11:30 am

MÉDECINS DU MONDE 世界の医療団 ÄRZTE DER WELT منظمة أطباء العالم
Γιατροί του Κόσμου DOKTERS VAN DE WERELD MÉDICOS DEL MUNDO
MÉDICOS DO MUNDO LÄKARE I VÄRLDEN DOCTORS OF THE WORLD

Fighting patent barriers: the patent opposition for Sofosbuvir

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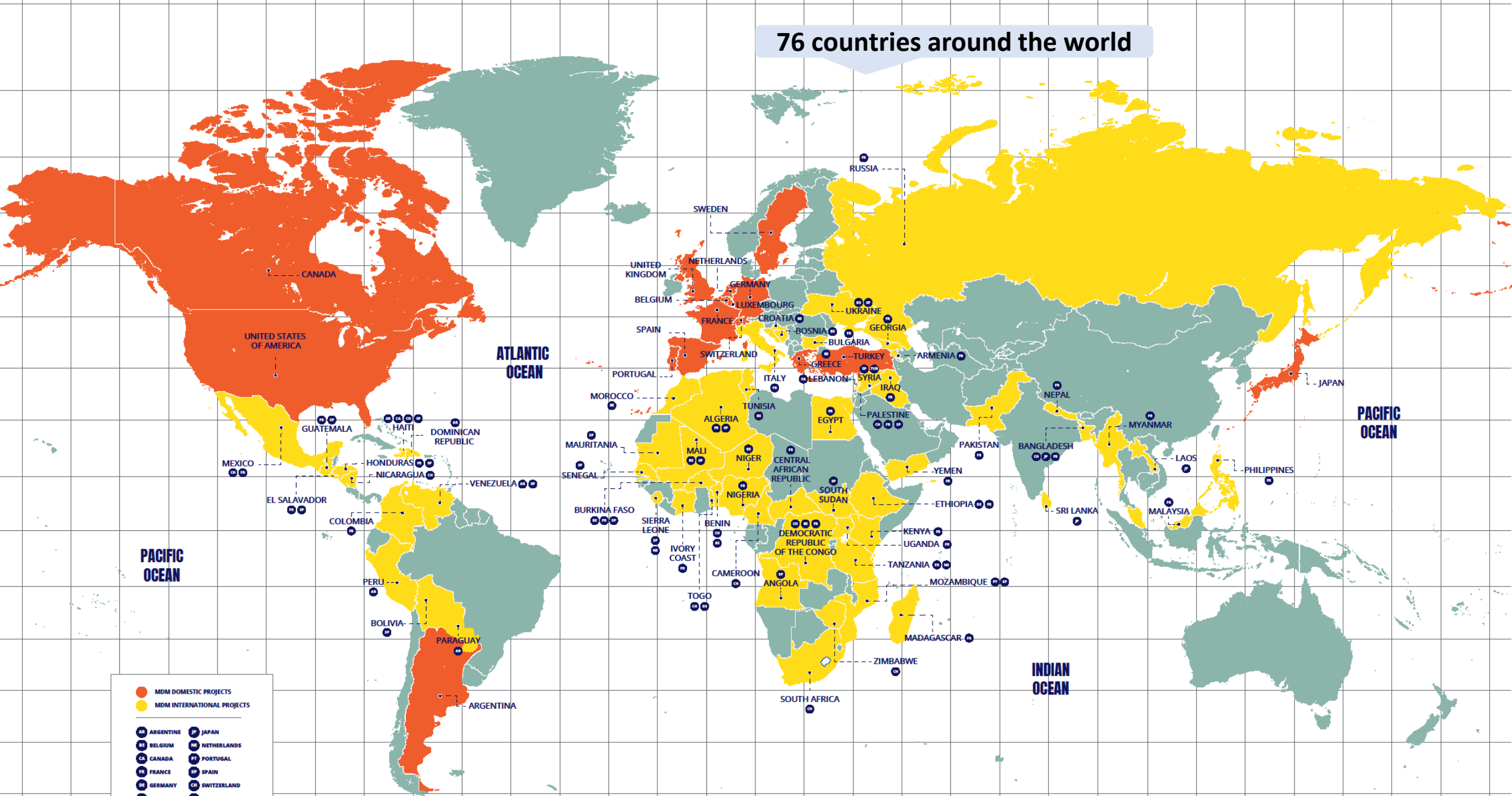
MÉDECINS DU MONDE NETWORK PROJECTS 2020

MÉDECINS DU MONDE - MÉDICOS DEL MUNDO - DOCTORS OF THE WORLD - DOKTERS VAN DE WERELD - LÄKARE I VÄRLDEN - ÄRTZE DER WELT - DÜNYA DOKTORLARI DERNEGI - MEDICOS DO MUNDO - Γιατροί του Κόσμου - 世界の医療団 - DOKTEREN VUN DER WELT



2022: What we are planning

Advcocacy Community	**Promote joint UHC related activities**	• Coordinate participation to WHA 75 (2022) • Initiate process to extend and strengthen observatory report
	Improve Covid-19 health policies	• Continue promoting No Profit on Pandemic ECI • Identify and initiate advocacy activities for greater access to Covid-19 vaccines, diagnostics, and treatment
	Specify A2M activities	• Focus on few unique selling point activities regarding IP and patents • Intensify cooperation with European Alliance for responsible R&D and affordable medicines
	Address Climate Crisis and Health as network	• Agree on common CC&H strategy and roadmap • Active participation of the next COP and follow up of COP working sessions • Identify focal actors and activities related to CC&H
	Networkwide cooperation	• Focus on inter-community activities/cooperation with other communities (e.g. joint observatory report) • Cooperation with ComCom to better promote advocacy activities
	Internal management	• Propose quick response protocol and review of GVP • Evaluation of current work platform (basecamp) and possible alternatives (e.g. Teams) • Agree on guideline for network memberships

- **Opposition against European Patent n°2604620**
- **(“Sofosbuvir base compound”)**

Patent oppositions and access to Sofosbuvir in Europe

In February 2015, Médecins du Monde filed a patent opposition at the European Patent Office (EPO) on the prodrug patent for Sofosbuvir, a treatment for hepatitis C. A “prodrug” is the chemical formula of a drug which, once absorbed by the body, develops its therapeutic activity. Examiners recognized that the patent application did not describe in sufficient detail the exact arrangement of the mixture of molecules that leads to Sofosbuvir, among other several possible formulations. However, the examiners of EPO Opposition Division acknowledged that the mixture had an inventive step.

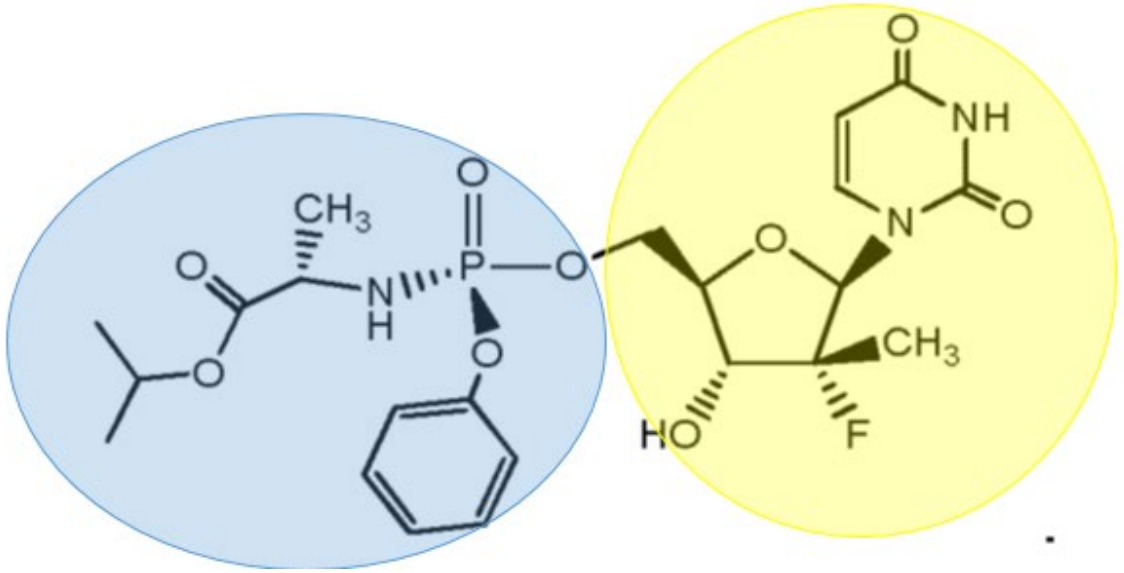
In March 2017, Médecins du Monde and other national and European civil society organizations filed a second patent opposition on Sofosbuvir compound. Even before the final decision of the Division of the EPO, which is expected for 2021, this opposition has already a positive result.
Indeed, in response to the arguments filed by Médecins du Monde and its allies in their opposition brief, Gilead Sciences has already decided to amend this second patent, by modifying the claims in favor of more restrictive wording, thus indirectly admitting the weakness of its patent application.

Doctors of the World has already opposed to a major Sofosbuvir patent in February 2015. In October 2016, European Patent Office has stated that Gilead did not have met all the requirements for its patent application. This decision led to cancel Sofosbuvir chemical formula from the scope of the patent. It means that Sofosbuvir as a drug is no more protected by the patent. Yet, Gilead keeps on requesting high prices for a drug no more protected as initially; and governments keep on accepting paying high prices.

"2015 opposition was the ever first opposition proceeding against a drug patent carried out by civil society in Europe. We have demonstrated that we could ***successfully invite ourselves in the patent system in Europe to raise non-compliance with patent regulation***

Sofosbuvir

- Sofosbuvir, a NS5B inhibitor, is the active principle of Sovaldi®
- It is comprised of two parts, a nucleoside analogue moiety and a phosphoramidate moiety:



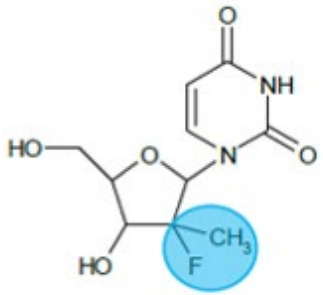
Phosphoramidate

Nucleoside analogue

Sofosbuvir action

Patent EP2604620

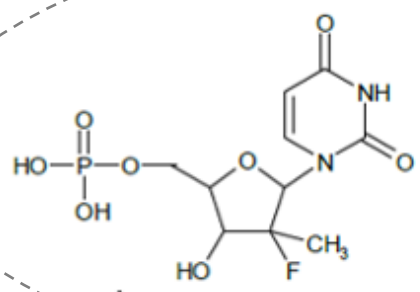
Base compound



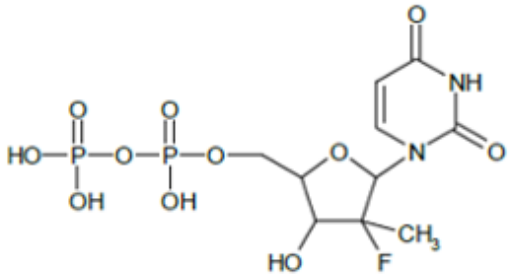
RO2433

Extracellular

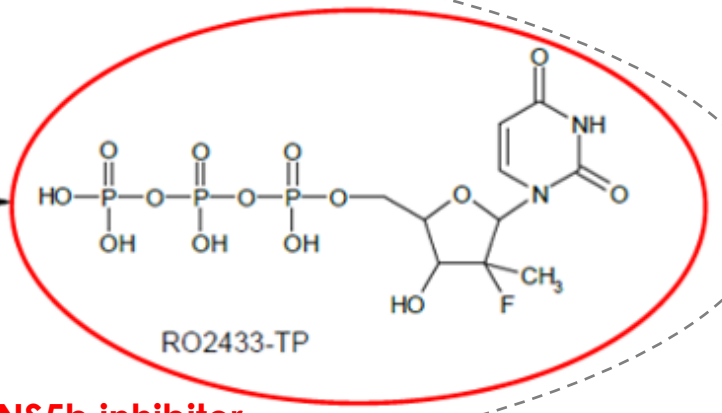
Intracellular



RO2433-MP

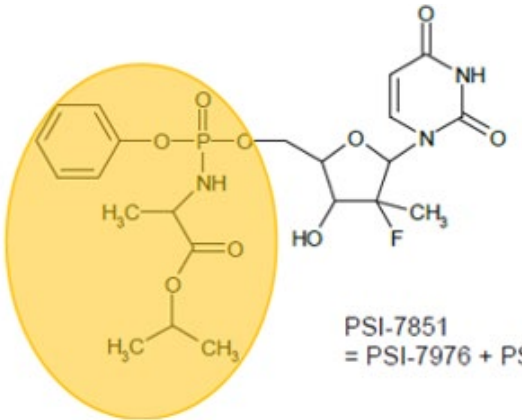


RO2433-DP



RO2433-TP

NS5b inhibitor



PSI-7851
= PSI-7976 + PSI-7977 (Sofosbuvir)

Sofosbuvir

Patent EP2203462

Base compound

Opposition against EP2203462

The opposition was first filed by **Médecins du Monde**, followed by oppositions by 9 other opponents, including the generic drug manufacturers Mylan, Teva and Actavis.

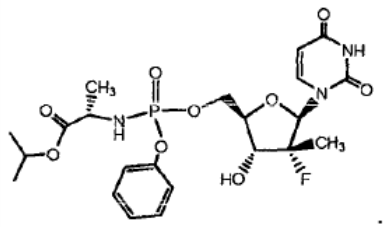
At the end of the oral proceedings, held in Munich, **the patent was maintained under amended form**.

Outcome of the opposition

- Claims 2, 3, 5 and 6 as granted have been canceled because their subject-matter extended beyond the content of the application as filed.
- Claims 1 and 4 have been upheld.
- The patent is thus said to be **maintained under amended form** (*i.e.* the claims as granted have been amended by canceling claims 2, 3, 5 and 6).
- Sofosbuvir is the compound forming the subject matter of claim 2, now canceled.

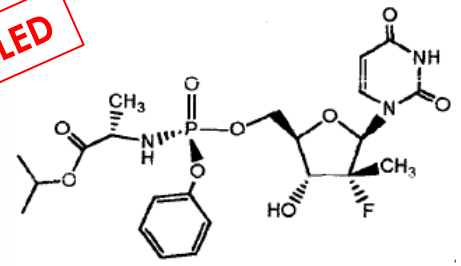
Claims

1. A compound represented by the formula



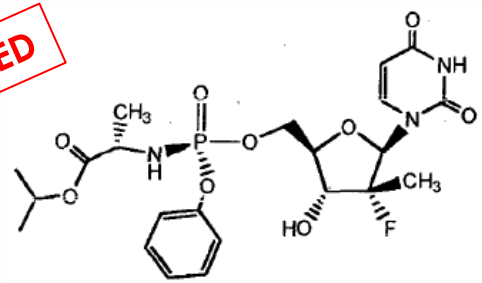
2. A compound represented by the formula

CANCELED



3. A compound represented by the formula

CANCELED



4. A composition comprising the compound of claim 1 and a pharmaceutically acceptable medium.
5. A composition comprising the compound of claim 2 and a pharmaceutically acceptable medium.
6. A composition comprising the compound of claim 3 and a pharmaceutically acceptable medium.

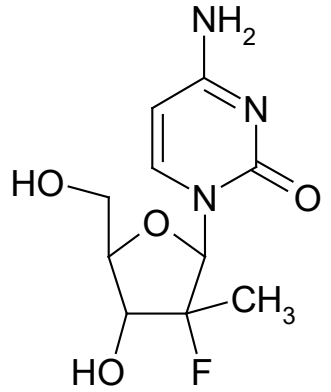
CANCELED

Base compound

Main arguments for the opposition

The patent was essentially filed to protect 2'-deoxy-2'-fluoro-2'C-methyl **cytidine** which was viewed by the applicant as a promising anti-HCV compound at the time the application was filed (see Clark *et al.,* (2005) J. Med. Chem. 48, 5504-5508).

In contrast, RO2433 (the base compound) was found to be **inactive** and is thus poorly covered by the patent. This gives rise to the following objections.



- **The subject-matter of the European patent extends beyond the content of the application as filed:**

The structure of certain claimed compounds is not disclosed as such in the application as filed.

- **Insufficient disclosure of the invention:**

The application does not disclose methods to prepare RO2433.

- **The subject-matter of the claims does not involve an inventive step:**

RO2433 is not shown to be endowed with a particular technical effect (to the contrary it is inactive by itself) and is further obvious in view of the prior art.

Base compound

The subject-matter of the European patent does not involve an inventive step

It could first be argued that RO2433 is not endowed with a particular technical effect and as such does not involve an inventive step.

Indeed, no experimental data which show that RO2433 would be effective in treating HCV infections are presented in the European patent, as the European patent only presents experimental data for the (2'R)-2'-deoxy-2'-fluoro-2'C-methyl cytidine.

In contrast, post-published data confirm that compounds covered by claim 6 as granted do not have any anti-HCV activity.

As such, Clark *et al,* (2005) J. Med. Chem. 48, 5504-5508, shows that compound 9 (2'-deoxy-2'-fluoro-2'-C-methyluridine, circled below) represented by the following formula is **not** active in the HCV replicon assay:

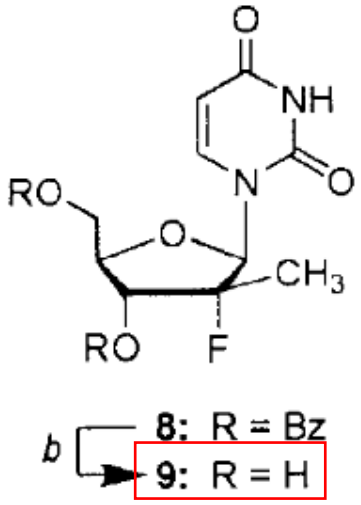


Table 2. Anti-HCV Activity and Cellular Toxicity of Compounds **1**, **9**, 2′-*C*-Methylcytidine (2′-*C*-MeCyd), and 2′-Deoxy-2′-fluorocytidine (2′-FdCyd)

	cpBVDV[a] (MDBK cells)		HCV replicon[b]	
compound	EC_{90} (μM)[b]	CC_{50} (μM)	EC_{90} (μM)	CC_{50}[c] (μM)
1	>100	>100	5.40 ± 2.6	>100
9	>100	>100	>100	>100
2-*C*-MeCyd	2.30 ± 0.1	>100	19.0 ± 5.7	>100
2-FdCyd	>100	>100	6.50 ± 1.6	>100

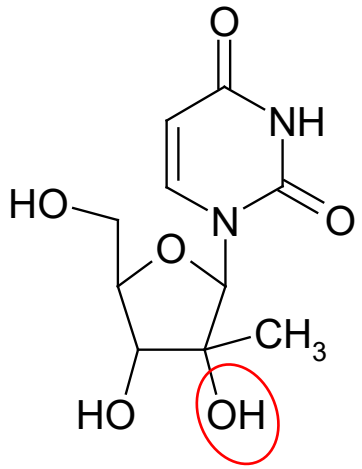
[a] cpBVDV = cytopathic BVDV. [b] 96 h, average of at least four experiments. [c] MTS CC_{50} was determined in a 4-day assay using the Celltiter 96 nonradioactive cell proliferation assay from Promega (Madison, WI).

Base compound

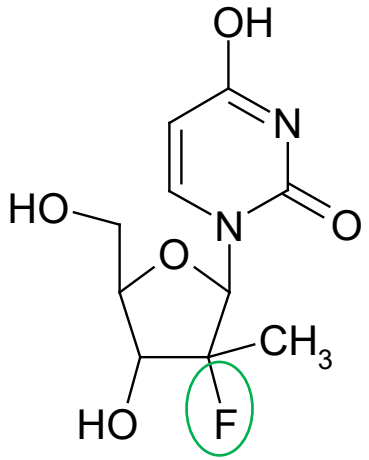
The subject-matter of the European patent does not involve an inventive step

Should be nevertheless considered that RO2433 involves a technical effect, this compound would still not involve an inventive step as it can be considered obvious in view of the prior art.

By way of example, it could be argued that RO2433 obviously derives from the following nucleoside useful in treating *Flaviviridae* infections (WO01/92282):



WO01/92282



RO2433

More particularly, it would be obvious to replace the hydroxyl group (circled in red) by a fluorine group (circle in green) having similar properties, thereby arriving at RO2433 without exerting an inventive skill.

CONCLUSIONS

Through these two initiatives, Médecins du Monde and its partner associations have demonstrated the fragility of patents and monopolies, on which manufacturers rely to demand unsustainable prices. Although these two oppositions do not, as such, allow the immediate production of generic versions of sofosbuvir, since it remains partially protected, they nevertheless weaken Gilead's claims.

In the first opposition the patent was not revoked but weakened, since sofosbuvir formulation is no longer protected by the patent.

The second opposition has a much stronger social and associative basis, since more than 30 organizations from 17 European countries have mobilized around a common political initiative.


LET'S GET TO WORK

NEXT STEPS

- A Task Force “Access to Medicines” connected to Universal Health is created inside MdM International Network.

- Advocacy Campaings as The Price of life and NO ES SANO.

- Inclusive work wit other NGOs and Professional Associations to advocate for universal acess to vaccines and new treatments for COVID19.

- Presence at World Health Assembly, International Forums and national events.

- In Spain, we are developing a study about the mechanism to fix prices at national level.

THANK YOU!

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