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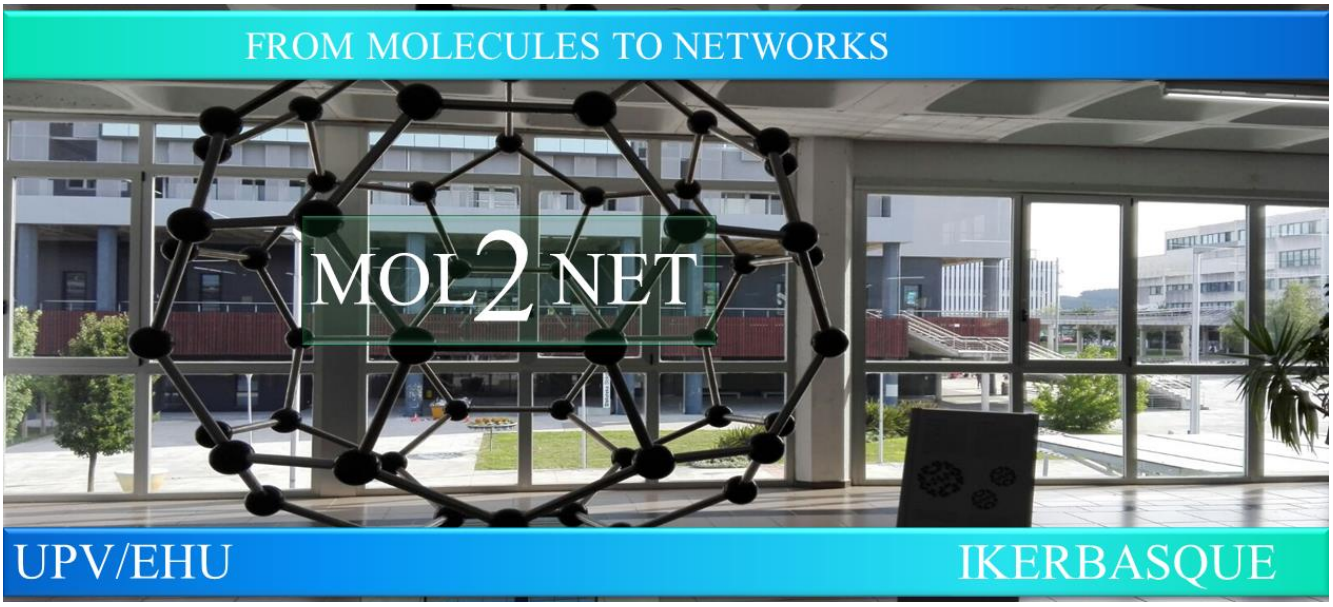

Stereochemical implications of remdesivir in combating the COVID-19

Jeremias Justo Emídio [a], Paulo Sérgio da Silva Pereira Author [a], Igor Mikael Alves de Araujo [a], Jéssica Paiva de Moura [a], Teresa Carolliny Moreira Lustoza Rodrigues [a], *Nikole Durand Trigueiro* [a], Alex France Messias [a b], Luciana Scotti [a b c].

[a] *Postgraduate Program in Natural and Synthetic Bioactive Products, Federal University of Paraíba, Health Science Center. Campus I, 50670-910, JoãoPessoa, PB, Brazil;*
[b] *Specialization Course in Aesthetics and Cosmetics – Integrated Technology and Research Center – CINTEP, Rua Deputado Geraldo Mariz, 849, Tambauzinho, João Pessoa - PB, CEP 58042-060*
c Teaching and Research Management - University Hospital, Federal University of Paraíba, João Pessoa, PB, Brazil.

Abstract.

The covid-19 is an infectious disease of the repertory tract caused by beta coronavirus, a disease that was considered a pandemic by the World Health Organization (WHO) in March 2020. Currently several vaccines are available for the prevention of covid-19, however few drugs have been shown to be effective in combating the current coronavirus, with remdesivir being the only approved drug Food and

Drug Administratio (FDA). The remdesivir has two diastereoisomers due to the presence of a chiral phosphorous atom in its molecule, and the diastereomer-(Sp) is used in the clinic.

Introduction

Severe acute respiratory syndrome (SARS-Cov-2), corresponds to an infection that has as etiological agent the human coronavirus, a disease called COVID-19, the virus was identified in December 2019 in Wuhan, Hubei Province, China (CIOTTI *et al*., 2020). The pandemic situation was rapidly declared throughout the world, and the pandemic situation was decreed by the World Health Organization (WHO) in March 2020, and it was said that in 2020 alone it infected 4,806,299 people, of which 318,599 (CIOTTI *et al*., 2020).

COVID-19 is a disease that affects the respiratory system, especially lungs, however the clinical picture comprises varied symptoms, from mild to severe, and infection is asymptomatic in the vast majority of people (WANG *et al*., 2020). Among the mostfrequent symptom sology can be mentioned: fever, cough and shortness of breath. However, due to the wide distribution of angiotensin 2 receptors (ACE2) in the body, various symptoms may occur, such as gastrointestinal symptoms (vomiting, diarrhea and abdominal pain), kidney, hepatic and central nervous system (WU *et al*., 2020). In patients with previous lung disease, multiple spots and opacity are often observed on chest X-ray (WANG *et al*., 2020).

In laboratory tests, it is very common that lymphocyte, eosinophil and hemoglobin counts are below the reference values, however, there may also be an increase in the count of leukocytes, neutrophils and elevated serum concentrationsof CRP, LDH, AST and ALT (LIPPI: PLEBANI, 2019). There may also be changes in the sea disease of cytokines such as (IL)-2, IL-7, stimulator factor of granulocyte colonies, interferon-γ-10 inducible protein, tumor necrosis factor-α, chemotactic protein of monocytes 1 and inflammatory protein of macrophages 1-α (HUANG *et al*., 2020; CIOTTI *et al*., 2020).

Due to the effort steam of the scientific community, there are currently several vaccines approved to combat COVID-19, but few drugs have been shown to be effective for the treatment of the disease. Remdesivir represents the only drug approved by the Food and Drug Administratio (FDA), in the virus, this compound in its activeform is capable of inhibiting RNA polymerase dependent on RNA, soon avoids viral replication (BIGLEY *et al*., 2020). In view of the above, the present study has as main objective to analyze the differences in the pharmacological activity of the two diastereoisomers of the remdesivir.

Materials and Methods

The present work was developed through a literature review in the main academic journals available on the internet, as a search strategy were used the descriptors: "COVID-19" and "isomer drugs used in the treatment of COVID-19".

Results and Discussion

The remdesivir corresponds to a prodrug dthe class of nucleotides phosphasides (ProTide), in other words is a nucleoside phosphate aryl or phosphonate masked with an amino acid ester ligated by a bond between nitrogen and phosphorus (SLUSARCZYK: SERPI: PERTUSATI, 2018). Andss the pharmacological class is more effective when employedat lower doses than those used and m its contraparts of unmasked nucleosides, because andat reduced concentrations it is observeda m aior cellular availability and metabolic activation profile (BIGLEY *et al*., 2020).

In the chemical structure of remdesivir is a chiral phosphorus atom, and currently the diastereomer-(Sp) corresponds to the compound used in the clone, however, this is not the active form of the drug (BIGLEY *et al*., 2020). It is known that inhibition of viral replication occurs due to the action of nucleotide triphosphate derived from remdesivir by inhibiting rna essential RNA dependent on RNA (EASTMAN *et al*., 2020; BIGLEY *et al*., 2020).

The mechanism of activation of remdesivir occurs in the intracellular environment through spontaneous cycling after enzymatic hydrolysis of the amino acid carboxylate ter, according to scheme 1 (BIGLEY *et al*., 2020). Then the intermediate phosphadate goes through a process of hydrolis and catalyzed by a protein d the group of the histidine triad (Hint1), thus the remdesivir monophosphate is produced, which is then phosphorylated by enzymes to the active final triphosphate compound (EASTMAN *et al*., 2020).

With regard to catalyst enzymes d theactivation of remdesivir, carboxylato esterase 1 (CES1) and catepsin A (CatA) are considered themain responsible for the initial reactions (BIGLEY *et al*., 2020). Studies indicate that the expression of these enzymes occurs in a variety of ways in different human tissues, also showing that (CatA) has a strong predilection for the hydrolysis of the diastereomer (Sp) of the prodrug (BIGLEY *et al*., 2020). On the other hand, CES1 mostly hydrolysis diasteromer (Rp), however, this enzyme has extremely limited tissue distribution (BIGLEY *et al*., 2020). In the case of COVID-19, it is very difficult to explore these characteristics, since the infection can manifest itself in different tissues, however, it is believed that the wide distribution of antiviral activity may be beneficial in some situations (BIGLEY *et al*., 2020; EASTMAN *et al*., 2020).

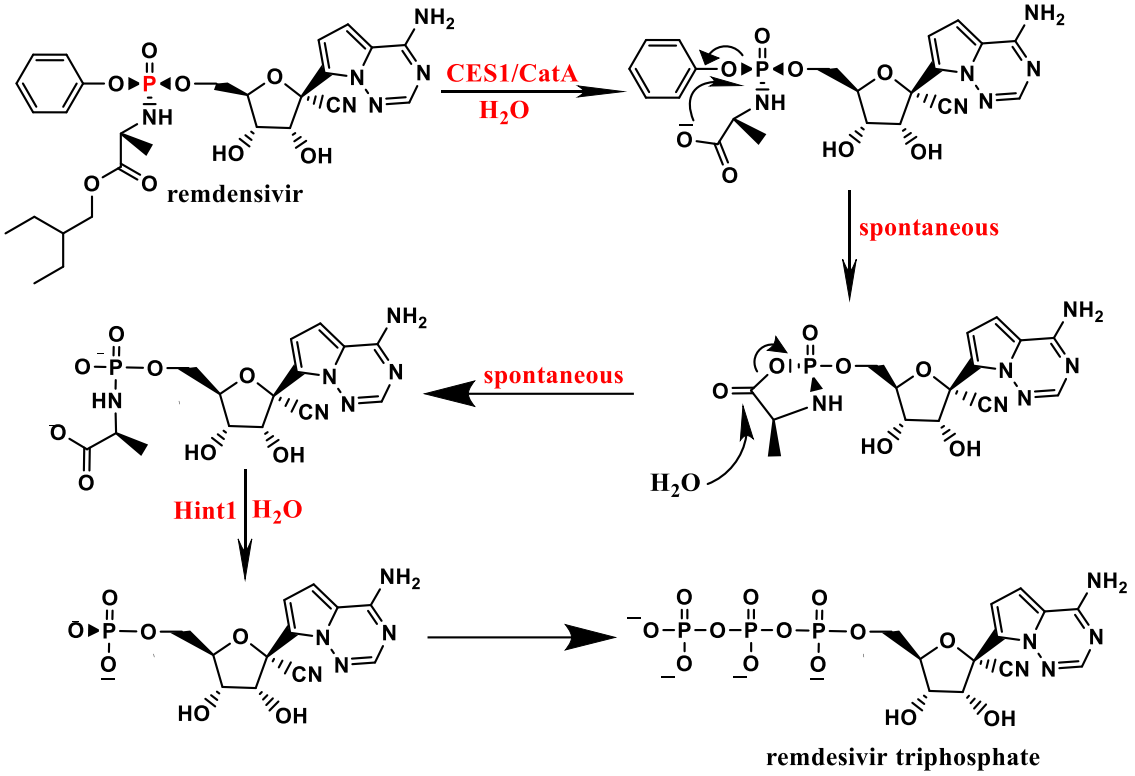

Figure 1: Theactivation of remdesicome in biological conditions, adapted from BIGLEY *et al*., 2020.

The antiviral activity of remdesivir, interacting esteramente with RNA-dependent RNA polymerase was *demonstrated in vitro against* various sceptical strains of coronavirus, among them: SARS, MERS and the current bandta coronavirus (EASTMAN *et al*., 2020). By means of biomicas, it was confirmed that the mechanism of action of the drug induces the late termination of the RNA chain, thus inhibiting viral replication (EASTMAN *et al*., 2020).

It wasalso observed, *through in vitro studies*, that the diastereomers (Rp) and (Sp) of remdesivir are also effective antiviraland that the effectiveness of inhibition did not depend on the typed diastereomers, but rather on the tissue studied. Thessim, it has been demonstrated that the diasteromer-(RP) of remdesivir may have some clinical importance in the fight against covid-19 (MACKMAN *et al*., 2017; BIGLEY *et al*., 2020).

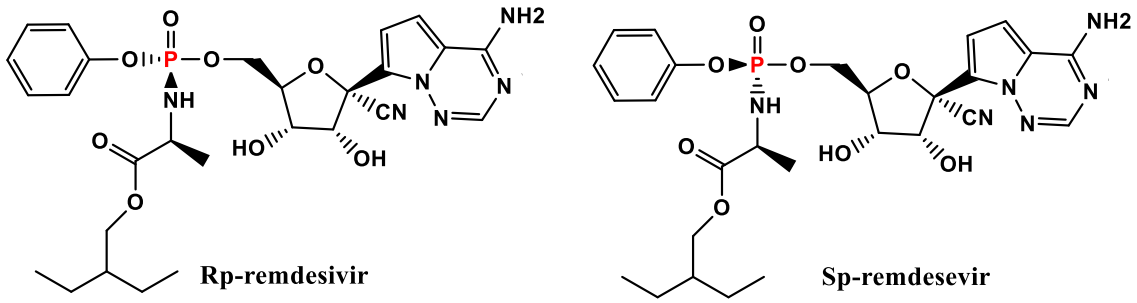

Figure 2: Chemical structure of the two isomers of the remdesevir, adapted from BIGLEY *et al*., 2020.

Conclusions

From the analyzed studies, it is evident the importance of knowing the implications inherent to stereochemistry in the pharmacological effect of drugs. Since small structural differences can cause major changes in the biological activity profile of a molecule, such as remdesivir, where the stereochemistry of the phosphorus atom present in the compound impacts the activation profile and, consequently, on pharmacological activity, finally, it should be noted that this will not always have a significant clinical repercussion (BIGLEY *et al*., 2020).

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