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Review

Antivirals Effective toward SARS-CoV-2

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Abstract

The review presents the basic data on the chemical compounds manifesting pronounced activity against SARS-CoV-2, the causative agent of the COVID-19 pandemic. The compounds are characterized with their chemical structure, and experimental anti-coronavirus activity *in vitro* (in cell cultures) and *in vivo* (in laboratory animals). The existing data on their clinical use in the treatment of patients with COVID-19, double-blind trials included, occupies an important place and are object of discussion on the therapeutic effectiveness of antivirals.

Keywords: SARS-CoV-2, COVID-19, antivirals, chemotherapeuc agents

Резюме

Обзорът обхваща основните данни върху химическите съединения, показващи отчетлива активност срещу SARS-CoV-2, причинител на пандемията от COVID-19. Съединенията са охарактеризирани с химическата им структура и с експерименталната им анти-коронавирусна активност *in vitro* (в клетъчни култури) и *in vivo* (в лабораторни животни). Наличните данни относно приложението им в клиниката за лечение на пациенти болни от COVID-19, включително в изпитания по схемата double-blind, заемат широко място и са обект на обсъждане за терапевтичната им ефективност като антивирусни средства.

Introduction

The review encompasses the basic data on the chemical compounds manifesting pronounced activity against SARS-CoV-2, the causative agent of the COVID-19 pandemic. It started in the Chinese 11-million city of Wuhan where the first cases of the disease were officially announced on December 31st, 2019 and gradually spread throughout the world. Some of the countries that currently have the highest COVID-19 morbidity rate are the USA, Italy, Spain and France. It may be said that the epidemic in China is over. In comparison with China, the morbidity rates in Europe and the USA are higher which could be explained by two factors: (a) the higher age of the population and (b) the inadequate level of the quarantine. The quarantine turned out to be the main line of defense against this pandemic. The same could be said about the SARS epidemic in 2002-2004. During that epidemic effective antivirals, anti-inflammatory agents and specific serotherapy were absent. Within the period between the SARS-CoV-1 epidemic and the COVID-19 pandemic, including the initial few weeks of the pandemic, a significant amount of work for the search of effective anti-coronavirus antivirals was carried out. They are presented in this review.

Ivermectin

Ivermectin [IM] is a broad-spectrum anti-parasitic substance. This US Foot-and Drug Administration (FDA)-approved drug is a mixture of mainly avermectin H2B1a with some avermectin H2B1b (Gonzalez Canga *et al*., 2008). The avermectins are bacterial marcrolides isolated from *Streptomyces avermitilis*.

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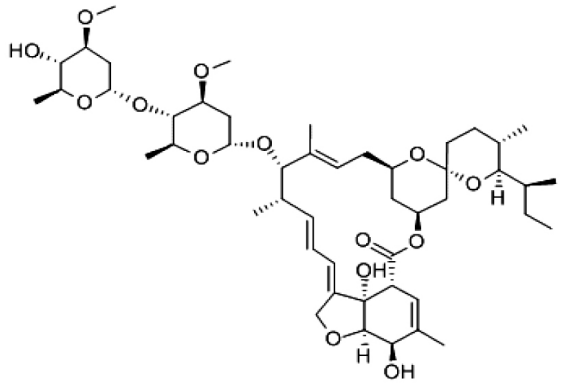


Formula: $C_{48}H_{74}O_{14}$ (22,23-dihydroavermectin B1a); $C_{47}H_{72}O_{14}$ (22,23-dihydroavermectin B1b); **Molar mass:** 875.1 g/mol

IM is a medication used to treat many types of parasite infections. This includes head lice, scabies, river blindness, strongyloidiasis, trichuriasis, ascariasis, and lymphatic filariasis. It can be taken by mouth or applied to the skin for external infestations. Use in the eyes should be avoided.

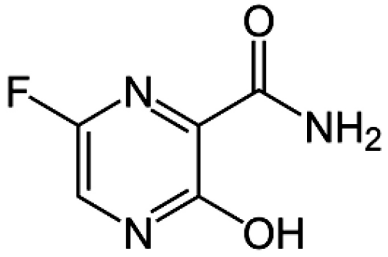
The compound manifests activity *in vitro* against a broad range of viruses: influenza A (Gotz *et al*., 2008), venezuelian equine encephalitis virus (Lundberg *et al*., 2013), dengue virus (Wagstaff *et al*., 2012; Tay *et al*., 2013), flavi- (Mastrangelo *et al*., 2012) and HIV-1 (Mastrangelo *et al*., 2012). On the model of HIV-1 IM inhibits the interaction between the integrase protein and the importin α/ß1 heterodimer responsible for integrase protein import (Wagstaff *et al*., 2011). Besides, IM inhibits nuclear import of viral and host cell proteins of SV40 and dengue virus (Wagstaff *et al*., 2011, 2012), limits infection by dengue virus, WNV, VEEV and influenza virus, based on the reliance on importin α/ß1 (Cally *et al*., 2012; Jans *et al*., 2019). IM was effective versus pseudorabies virus both *in vitro* and *in vivo* (in mice) (Lv *et al*., 2018). The compound was ineffective versus Zika virus in mice (Ketkar *et al*., 2019). Importantly, IM included in a double-trial against dengue infection via single daily oral dose, demonstrated to be safe and resulted in a significant reduction in plasma levels of viral NS1 protein, but no change in viremia or clinical benefit (Yamasmith *et al*., 2018).

IM was tested vs SARS-CoV-2 in Vero/hSLAM cells, infected at MOI 0.1 (Cally *et al*., 2020). After virus adsorbtion lasting 2 hours, the compound was added at a concentration 5 μM. A reduction by 93% of the extracellular and 99.8% of the intracellular viral RNA was established. At the 48th hour this effect increased to an approximately 5000-fold reduction of viral RNA as compared to the control samples. No further diminishement of viral RNA was recorded at the 72nd hour. IM was without cellular toxicity during this period of time. Detection of SARS-CoV-2 was carried out using a TaqMan Real-time RT-PCR assay.

On the base of these results, demonstrating the very high effectiveness of IM versus SARS-CoV-2, and its FDA-approval as anti-parasitic agent, the compound warrants further investigation for possible benefits in humans.

Favipiravir

Among antivirals studied toward SARS-CoV-2 favipiravir (6-fluoro-3-hydroxy pyrazine-2-carboxaide; favilavir, T-705, favipira; Avigan©), developed by the company „Fujifilm Toyama Chemical" (Fujifilm's daughter company), stands out by its effectiveness.



Formula: $C_5H_4FN_3O_2$; **Molar mass:** 157.10 g/mol

Favipiravir inhibits the replication *in vitro* of various RNA viruses – alpha-, flavi- (yelow fever virus, WNV), noro-, bunya-, influenza, filo- (ebola-), rhabdo- (rabies), arena-. It is remarkable that in experiments conducted *in vivo* (in laboratory animals) favipiravir has shown an unusually large scope activity: against influenza viruses, alphaviruses, flaviviruses (West Nile virus, yellow fever virus), bunyaviruses (Rift Valley virus), arenaviruses, picornaviruses (foot-and-mouth disease virus, enteroviruses) (Furuta *et al*.,.2009, 2013; Caroline *et al*., 2014). Favipiravir has showed limited efficacy against Zika virus and rabies virus (Mumtaz *et al*., 2016).

This compound is selective inhibitor of the viral RNA-dependent RNA polymerase (Jin *et al*., 2013). Its active form is phosphorilased - favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP). Favipiravir-RTP is available in both oral and intravenous formulations (Baranovich *et al*., 2013; Guedj *et al*., 2018). Favipiravir does not inhibit RNA or DNA synthesis in mammalian cells and is not toxic to them (Furuta *et al*., 2009).

Been approved in Japan as anti-influenza drug in 2014, in 2015 the compound was included

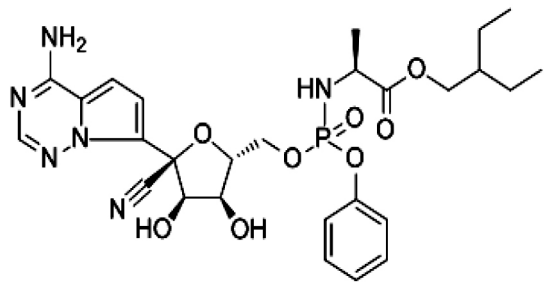
in phase III of a double-blind trial. China also registered favipiravir as anti-flu drug. However, favi-piravir (a) has not been shown to be effective in primary human cells, casting doubt on its efficacy in influenza treatment, and (b) animal experiments showed the potential for teratogenic effects on fetuses. For these reasons favipiravir registration was limited only in Japan. In 2015 FDA completed a Phase III clinical trial studying the safety and efficacy of favipiravir in the treatment of influenza (Smee *et al*., 2019; Yuoon *et al*., 2019).

Some research has been done suggesting that in mouse models favipiravir may have efficacy against Ebola. However, its efficacy against Ebola in humans is unproven (Fink, 2015; Cohen, 2015; Sissoko *et al*., 2016).

In China the drug was approved for use in clinical trials for treating COVID-19 pneumonia. This started with experimental treatment in February 2020 (Li and De Clercq, 2020; Cai *et al*., 2020; Dong *et al*., 2020). Clinical trials in Wuhan and Shenzhen on 340 patients, including a group of 80 divided in two – treated with favipiravir and with other means, demonstrated promising results: shortening of the illness, improvement of the clinical state in 91% of the ills, and in 62% of the treated by other means. On 17 March 2020, Chinese officials suggested that Favipiravir seemed to be effective in treating COVID-19 in Wuhan and Shenzhen (Hayden and Shindo, 2019).

On 22 March 2020 Italy has approved the drug for experimental use against COVID-19 and has begun conducting trials in 3 regions most affected by the disease. The Italian Pharmaceutical Agency, however, has reminded the public that the existing evidence in support of this drug is scant and preliminary (AIFA, 2020).

Remdesivir



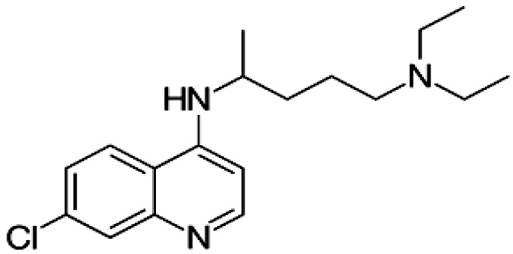
Formula: $C_{27}H_{35}N_6O_8P$;
Molar mass: 602.585 g/mol

Remdesivir (GS5734) is a novel antiviral drug in the class of nucleotide analogs. It is prodrug converted in the active structure which incorporates into nascent viral RNA chains and causes their pre-mature termination (Brunk, 2020).

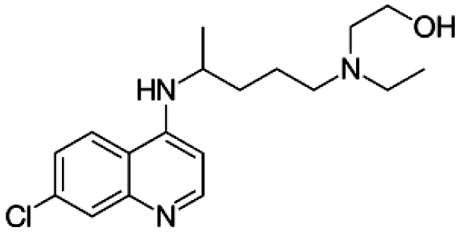
It was developed by Gilead Sciences as a treatment for Ebola virus disease and Marburg vi-rus infections (Lo *et al*., 2017). The compound possesses a large antivirus spectrum, showing antivi-ral activity against other single stranded RNA viruses, the paramyxoviruses respiratory syncytial virus, Nipah virus and Hendra virus, Junin virus, Lassa fever virus, and the coronaviruses (including MERS and SARS viruses) (Sheahan *et al*., 2017; Agostini *et al*., 2018; Brunk, 2020). In experiments *in vivo* in mice infected with MERS-CoV significantly decreased the lung virus titer, improved the lung function and diminished pathological damages in the lung tissue. Based on the success against other human coronavirus infections remdesivir was tested on SARS-CoV-2. In cell culture experiments the compound manifested a very high activity – selectivity index (SI) SI >129.87 (EC50 0.77 μM, CC50 >100 μM) (Dong *et al*., 2020). This was confirmed in *in vivo* testing. The remdesivir producer Gilead provided remdesivir to physicians who treated an American patient infected with SARS-CoV-2 in Snohomish County, Washington (Holshue *et al*., 2020) and then provided the compound to China to conduct a pair of trials in infected individuals with and without severe symptoms.Two double-blind trials were started (Johnson, 2020). The one which will end in April this year, started with 200 mg in the first day, followed by a 9-days course by 100 mg.

The compound has veterinary application for the treatment of feline coronavirus-induced infectious peritonitis (Addie, 2020).

Chloroquine/Hydroxychloroquine



Formula: $C_{18}H_{26}C1N_3$



Formula: $C_{18}H_{26}C1N_3O$

Chloroquine (Resochin©; chloroquine phosphate, Aralen©) is a medication primarily used to prevent and treat malaria in areas where malaria remains sensitive to its effects. Its potential antiviral activity was established by Savarino *et al*. (2006). Earlier, a research team of Rega Institute of Microbiologhy in Loeven showed effectiveness of the compound in cell culture test vs SARS-CoV-1. Screening study in cell cultures vs human coronaviruses SARS-CoV-1, SARS-CoV MERS and human CoV 229E demonstrated a marked activity of chloroquine, superior as compared with the anti-HIV-1 compounds lopinavir and ritonavir (de Wilde *et al*., 2014). Recently chloroquine manifested a very pronounced inhibitory effect on the replication of SARS-CoV-2 in cell culture study: EC50 1.13 μM and CC50 >100 μM,. SI >88 (Wang *et al*., 2020).

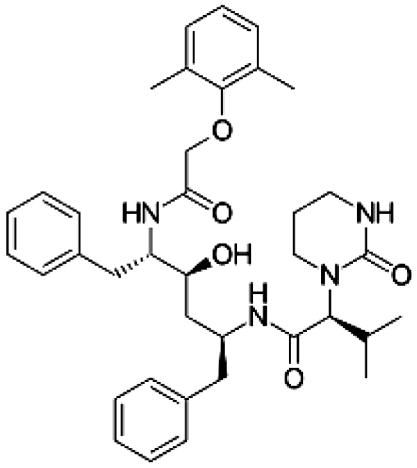
As concerns the mode of antiviral effect of chloroquine, it was established that chloroquine impaired the release of the virus from the endosome or lysosome. As a consequence, the virus is unable to release its genetic material into the cell and to replicate (Fredericksen *et al*., 2002). Besides, chloroquine acts as a zinc ionophore, that way allowing extracellular zinc to enter the cell and to inhibit viral RNA-dependent RNA polymerase (Velthuis *et al*., 2010; Xue *et al*., 2014).

In late January 2020 Chinese medical researchers stated that chloroquine have "fairly good inhibitory effects" on the SARS-CoV-2 virus (Wang *et al*., 2020) and requests to start clinical testing were submitted. Chloroquine has been approved by Chinese, South Korean and Italian health authorities for the experimental treatment of COVID-19. These agencies noted contraindications for people with heart disease or diabetes.

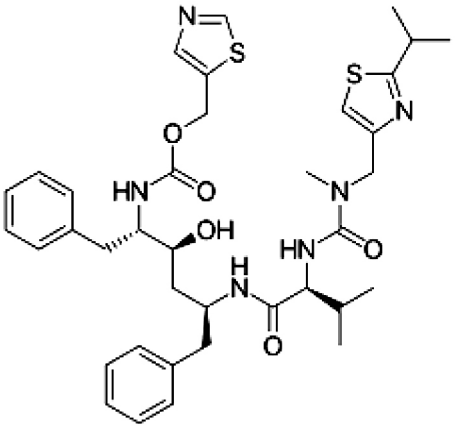
Hydroxychloroquine sulphate (Plaquenil©), is used to treat malaria in areas sensitive to chloroquine. Hydroxychloroquine is being studied as an experimental treatment for COVID-19, not been approved by FDA (Grady *et al*., 2020). The experimental treatment is authorized only for emergency use for people who are hospitalized but not included in a clinical trial. On 1 April 2020, the European Medicines Agency issued guidance that chloroquine and hydroxychloroquine are only to be used in clinical trials or emergency use programs (Corteliani *et al*., 2020).

Caletra (lopinavir/ritonavir)

Anti-HIV combination **caletra (lopinavir + ritonavir)**, a medication including two compoundes proved to be HIV-proteas inhibitors,



manifested an activity against SARS-CoV-1. A study on 80 patients comparing caletra to lopinavir and ritonavir applied individually found that it significantly reduced viral clearance time to four days, compared with eleven days for the control group, and that 91.43% of patients had improved clearence time scans with few side effects. The limitation of this study is that it was not a randomized double-blinded placebo-controlled clinical trial (Cao *et al*., 2020).



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