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Chemical Analysis of Anti-Covid Medications

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ABSTRACT

At the end of 2019, a novel virus causing severe acute respiratory syndrome spread globally. There are currently no effective drugs targeting SARS-CoV-2. In this study, based on the analysis of numerous references and selected methods of computational chemistry, the strategy of integrative structural modification of small-molecules with antiviral activity into potential active complex molecules has been presented. Proposed molecules have been designed based on the structure of triterpene oleanolic acid and complemented by structures characteristic of selected anti-COVID therapy assisted drugs. Their pharmaceutical molecular parameters and the preliminary bioactivity were calculated and predicted. The results of the above analyses show that among the designed complex substances there are potential antiviral agents directed mainly on SARS-CoV-2.

KEYWORDS: *virus, anti-COVID, antiviral, drugs, SARS-CoV-2, computational, chemistry*

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INTRODUCTION

Remdesivir has become an important compound for the treatment of COVID-19. Here, we describe the catalytic asymmetric synthesis of this anti-COVID-19 drug. First, the P-racemic phosphoryl chloride is synthesized in a facile procedure. Then, it is possible to obtain the protected remdesivir via the organocatalytic asymmetric phosphorylation of protected nucleoside GS441524 with P-racemic phosphoryl chloride catalyzed by chiral bicyclic imidazole. Finally, remdesivir is easily prepared by deprotection.

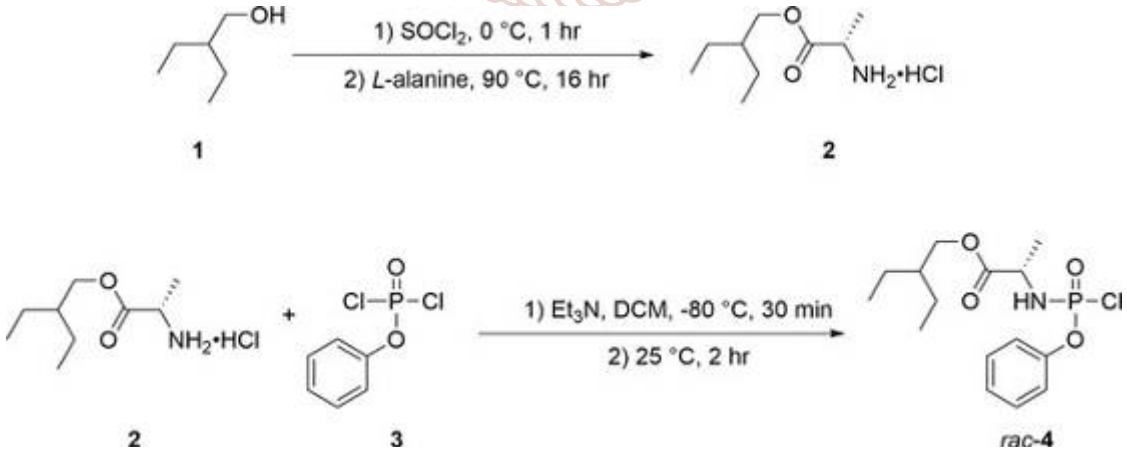


Fig.1. Basic Protocol 1: Synthesis of 2-ethylbutyl (chloro(phenoxy)phosphoryl)-L-alaninate rac-4

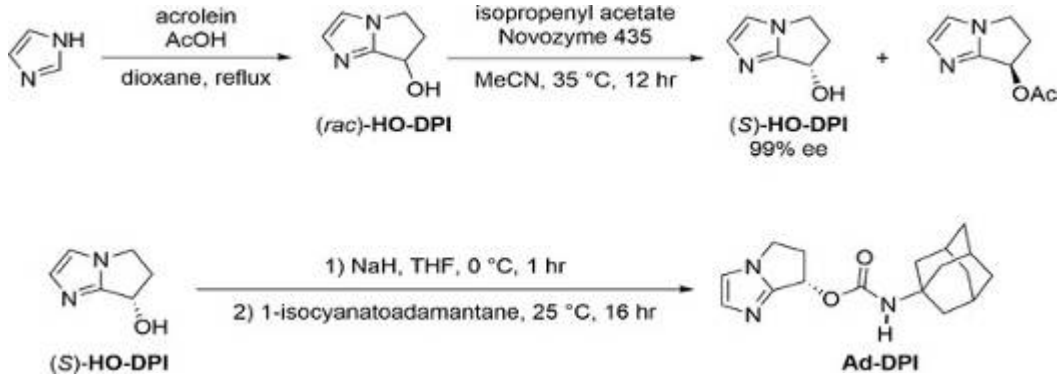


Fig.2. Basic Protocol 2: Synthesis of chiral bicyclic imidazole Ad-DPI

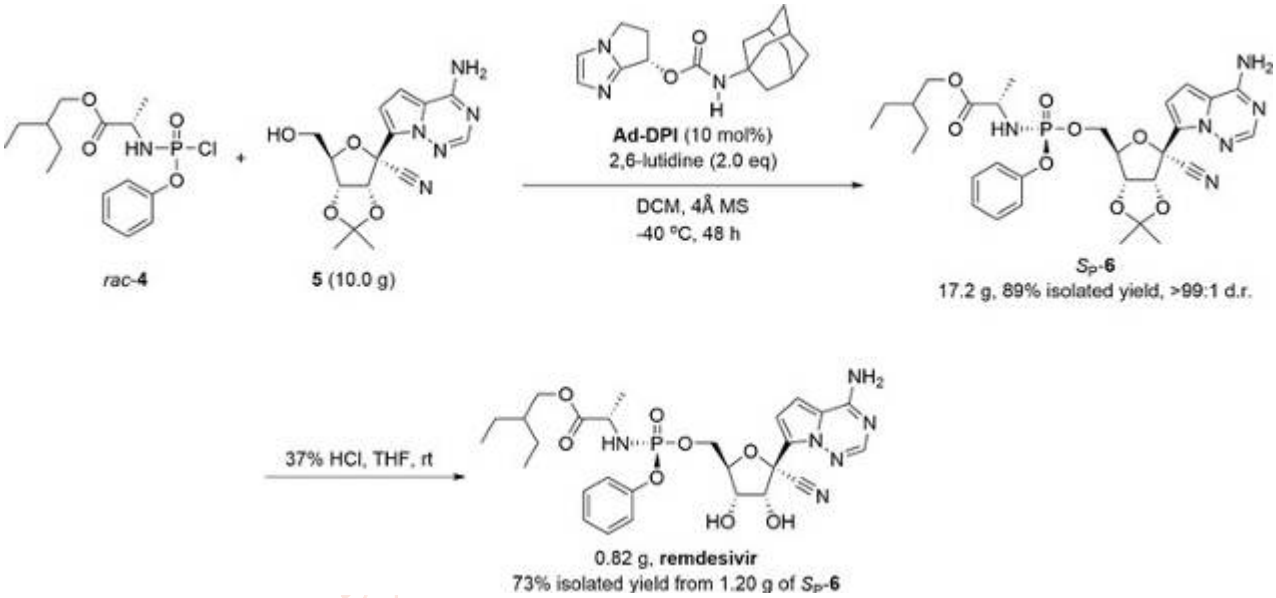
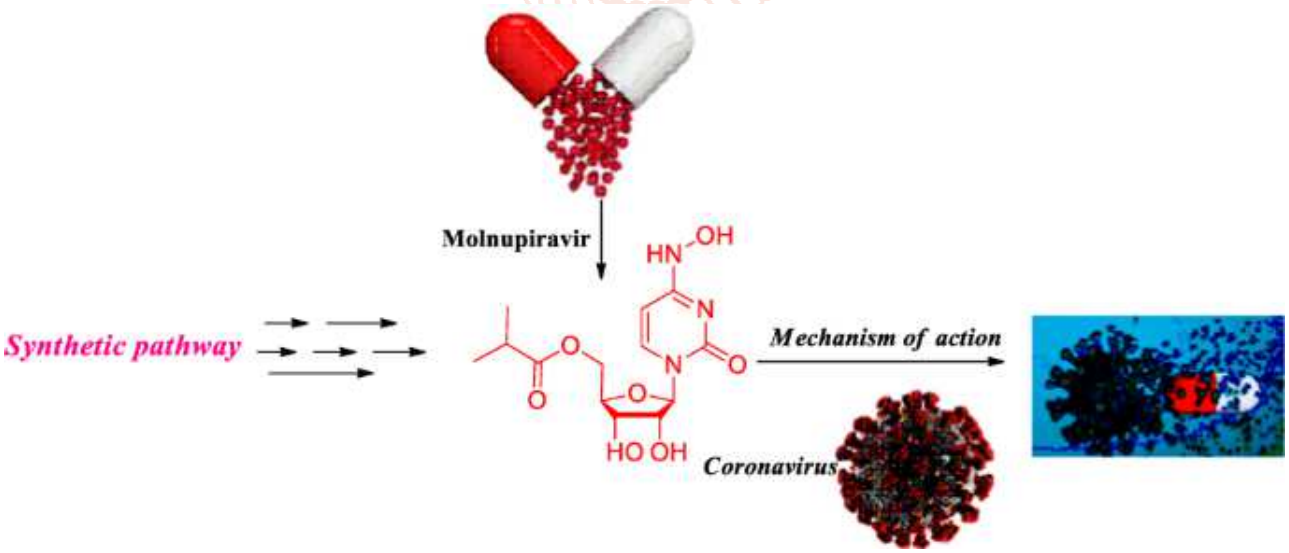


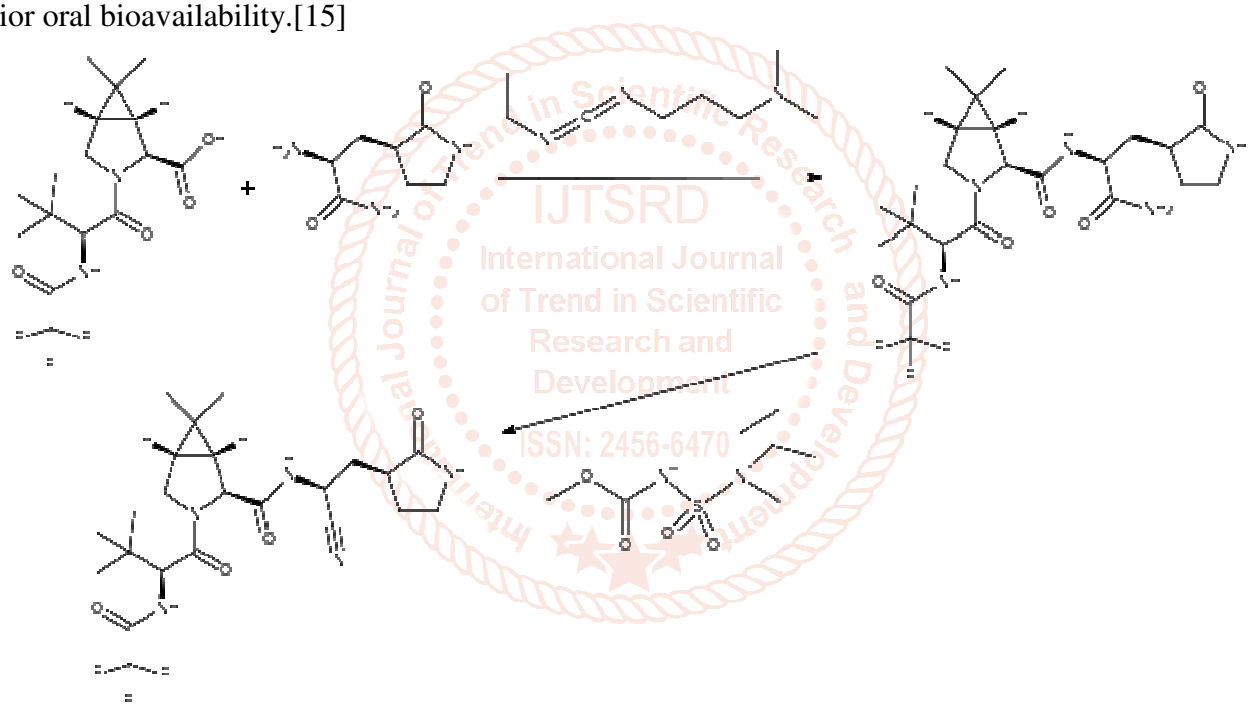
Fig.3. Basic Protocol 3: Synthesis of remdesivir.

During the COVID-19 pandemic, various drug candidates have been developed, molnupiravir (MK-4482 and EIDD-2801), which is a new orally anti-viral agent under development for the treatment of COVID-19, is under study in the final stage of the clinical trial. Molnupiravir enhances the replication of viral RNA mutations in animals and humans. [1] Due to the high demand for the synthesis of this drug, it was essential to develop an efficient and suitable synthetic pathway from raw material. In this study, molecular docking analysis on molnupiravir is examined also, the mechanism of action (MOA) and the recent synthetic pathway is reported.



Nirmatrelvir is an antiviral medication developed by Pfizer which acts as an orally active 3C-like protease inhibitor. It is part of a nirmatrelvir/ritonavir combination used to treat COVID-19. The combination is sold under the brand name Paxlovid.[2,3] Coronaviral proteases cleave multiple sites in the viral polyprotein, usually after there are glutamine residues. Early work on related human rhinoviruses showed that the flexible glutamine side chain in inhibitors could be replaced by a rigid pyrrolidone.[9][10] These drugs had been further developed

prior to the COVID-19 pandemic for other diseases including SARS.[11] The utility of targeting the 3CL protease in a real world setting was first demonstrated in 2018 when GC376 (a prodrug of GC373) was used to treat the previously 100% lethal cat coronavirus disease, feline infectious peritonitis, caused by feline coronavirus.[12] Nirmatrelvir and GC373 are both peptidomimetics, share the aforementioned pyrrolidone in P1 position and are competitive inhibitors. They use a nitrile and an aldehyde respectively to bind the catalytic cysteine.[13][14] Pfizer investigated two series of compounds, with nitrile and benzothiazol-2-yl ketone as the reactive group, respectively, and in the end settled on using nitrile.[15]Nirmatrelvir was developed by modification of the earlier clinical candidate lufotrelvir,[16][full citation needed][17] which is also a covalent protease inhibitor but its warhead is a phosphate prodrug of a hydroxyketone. Lufotrelvir needs to be administered intravenously limiting its use to a hospital setting. Stepwise modification of the tripeptide protein mimetic led to nirmatrelvir, which is suitable for oral administration.[3] Key changes include a reduction in the number of hydrogen bond donors, and the number of rotatable bonds by introducing a rigid bicyclic non-canonical amino acid (specifically, a "fused cyclopropyl ring with two methyl groups"[15]), which mimics the leucine residue found in earlier inhibitors. This residue had previously been used in the synthesis of boceprevir.[18] Tert-leucine (abbreviation: Tle) used in the P3 position of nirmatrelvir was identified first as optimal non-canonical amino acid in potential drug targeting SARS-CoV-2 3C-like protease using combinatorial chemistry (hybrid combinatorial substrate library technology).[4,5]The leucine-like residue resulted in loss of a nearby contact with a glutamine on the 3C-like protease.[15] To compensate Pfizer tried adding methane sulfonamide, acetamide, and trifluoroacetamide and discovered that of the three, trifluoroacetamide resulted in superior oral bioavailability.[15]



In the penultimate step a synthetic homochiral amino acid is coupled with a homochiral amino amide using the water-soluble carbodiimide EDCI as a coupling agent. The resulting intermediate is then treated with Burgess reagent, which dehydrates the amide group to the nitrile of the product.[3]

Nirmatrelvir is a covalent inhibitor, binding directly to the catalytic cysteine (Cys145) residue of the cysteine protease enzyme.[2]In the co-packaged medication nirmatrelvir/ritonavir, ritonavir serves to slow the metabolism of nirmatrelvir via cytochrome enzyme inhibition, thereby increasing the circulating concentration of the main drug.[6,7] This effect is also used in HIV therapy, where ritonavir is used in combination with another protease inhibitor to similarly enhance their pharmacokinetics.[18]

Discussion

When you catch Covid, your body releases a flood of chemicals to warn that you're under attack. This chemical alarm is called inflammation, and is vital for rallying your immune system to boot out Covid. But if you don't get rid of the virus quickly, then inflammation can spiral out of control and eventually damage vital organs such as your lungs. It's this excessive inflammation that kills. An anti-inflammatory steroid that already existed before Covid - dexamethasone - was the first drug proved to save the lives of people with Covid. It's given to seriously ill patients with breathing troubles - it cuts the risk of death by a fifth for patients on oxygen, and by a third for those on ventilators.[8,9]

It is also so cheap that it has become the go-to drug around the world - with everywhere from Brazil to China using it. Other anti-inflammatory drugs have been shown to work, including the steroid hydrocortisone and baricitinib, which is normally used in rheumatoid arthritis. There are more advanced and targeted anti-inflammatory drugs such as tocilizumab and sarilumab. Tocilizumab has been widely used in hospitals in China, India and Australia. These are also effective, but up to 100 times as expensive as dexamethasone. This has restricted their use - although they are still cheaper than an intensive care bed. Anti-inflammatories work best later on in the disease, but an asthma drug called budesonide has been shown to help vulnerable people with early Covid symptoms recover more quickly at home.

The quest for effective drugs to treat COVID-19 has been a priority since the outbreak of the disease. The clinical application of remdesivir has been greatly restricted by the need for intravenous administration, as well as unstable concentrations in plasma and variable antiviral activity in different organelles. Four neutralising antibodies (bamlanivimab, etesevimab, casirivimab, and imdevimab) have been approved by the United States Food and Drug Administration; however, their high cost and need for intravenous administration render them inaccessible to the public. Therefore, effective and economical oral drugs are the priority for the prevention and control of COVID-19, because they can be used after exposure to SARS-CoV-2 or at the first sign of COVID-19.Molnupiravir is an oral antiviral drug with β-d-*N*-hydroxycytidine (NHC) as the active ingredient, and has been jointly developed by Merck (Kenilworth, NJ, USA) and Ridgeback (Miami, FL, USA). NHC monophosphate can pair with adenine or guanine and induce lethal mutations during subsequent RNA synthesis; however, NHC does not terminate strand synthesis and is therefore resistant to the proofreading function of SARS-CoV-2 nsp14. Data from the phase 3 MOVe-OUT trial[10,11]

showed that treatment with molnupiravir reduced hospitalisation or mortality by approximately 50% compared with placebo in patients with mild or moderate COVID-19—a very promising finding given that more than 4·7 million deaths worldwide have been attributed to COVID-19 to date. Molnupiravir showed a stronger antiviral effect than remdesivir (50% inhibitory concentration [IC_{50}]: 0·3 μmol/L *vs* 0·77 μmol/L) and ideal toxicity (50% cytotoxic concentration [CC_{50}]>10 μmol/L) in vitro.

The phase 2 clinical trial also showed a promising result: no live virus could be isolated from patients who received 400 mg (n=42) or 800 mg (n=53) molnupiravir for 5 days, whereas live virus was isolated from 11·1% of patients in the placebo group (n=54; p=0·03). Moreover, molnupiravir has a favourable safety and tolerability profile. However, given that 7·3% of participants treated with molnupiravir were still hospitalised during a 29-day observation period—and the potential for molnupiravir, a mutagenic ribonucleoside, to be carcinogenic—the development of oral antiviral treatment for COVID-19 still needs further study. In addition to molnupiravir, four more oral anti-COVID-19 drugs are in phase 3 clinical trials: the 3CL protease inhibitors PF-07321332 (developed by Pfizer [New York, NY, USA]) and s217622 (developed by Shionogi [Osaka, Japan]), the RdRp inhibitor AT-527 (jointly developed by Roche [Basel, Switzerland] and Atea [Boston, MA, USA]), and the SARS-CoV-2 ACE2 and TMPRSS2 antagonist proxalutamide (initiated by Kintor Pharma [Suzhou, China]). While COVID-19 is prevalent, the combined use of immunomodulatory or anti-inflammatory agents, antivirals, and host-factor antagonists might be the optimal therapy for the disease. The emergence of affordable and powerful oral anti-COVID-19 drugs and the increased uptake of vaccination will bring hope for the end of the COVID-19 pandemic.[12,13]

Results

Department of Biotechnology's Centre of Innovative and Applied Bioprocessing (DBT-CIAB) at Mohali has planned a bouquet of research projects aimed at generating products that could be used for prevention, diagnosis or cure for the deadly COVID-19 infection that is currently sweeping over the entire world.

The plan has been designed so as to utilise the expertise of its scientists, who come from a diverse range of research backgrounds including chemistry, chemical engineering, biotechnology, molecular biology, nutrition, and nanotechnology.

Under the preventive platform, the Institute has planned to work on lignin-derived noble metal nanocomplexes for developing antiviral coating materials, and rose oxide-enriched citronella oil, carbopol and triethanolamine-formulated alcoholic sanitizer.[14,15]

Under the therapeutics platform, the effort will be focussed on polypyrrollic photosensitizers and their nanoformulations for antiviral photodynamic therapy, microbial production of immunomodulatory and antiviral fructan biomolecules, and development and commercial manufacturing of nasal spray kit to ease chest congestion suffered in corona infection, etc.

Under the drug discovery platform, in turn, the research will explore separation of therapeutic and valuable medicinal components from the peel and seeds of fruits and utilisation of natural garlic essential oil as an ACE 2 protein inhibitor for preventing SARS-CoV-2 invasion.

Besides, studies are to be conducted for development of lignin-derived nanocarriers (LNCs) with potential for antiviral drug delivery and using curcumin-fortified whey protein powder as a nutraceutical.

The researchers would endeavour to come out with products that are biocompatible, low cost and scalable and have set out with a timeline of six months to one year. The studies would be conducted in collaboration with chemical industries and other government laboratories with BSL-3 facility.[16,17]

Three main strategies for impeding the virus have emerged as the labs have turned to the current threat. One strategy is to find compounds like remdesivir and EIDD-2801 that gum up the virus's reproductive machinery when it enters a target cell. A second is to block the virus, like a bouncer outside a bar, from entering and infecting those cells in the first place. The third approach is to muffle the immune system's dangerously overactive response, a "cytokine storm" that can drown a victim in a mass of congestion and dying airway cells.

To find these drugs, researchers have turned to the Food and Drug Administration's list of some 20,000 compounds approved for human use and crawled through drug patent applications looking for compounds with promising mechanisms of action. The goal has been to find drugs that have been at least partly developed, avoiding years of making therapeutic molecules from scratch. The Milken Institute, a health advocacy think tank, counted 133 experimental COVID-19 treatments in mid-April. About 49 of these therapies are being rushed into clinical trials. Their effectiveness in people is not yet known, and scientists caution that such drugs, like other antivirals, are unlikely to be cures. But they could reduce symptoms enough to give patients' immune systems a chance to beat the virus on their own. All coronaviruses use the same mechanism to reproduce, which involves an enzyme called viral RNA polymerase, so Baric says that was an obvious target. The polymerase makes lots of mistakes as it copies the virus, and it relies on another enzyme, known as an exonuclease, to "proofread" and fix them. Remdesivir appears to disable the proofreading enzyme. Then the virus's copying factory becomes sloppy and produces fewer new viruses.

THREE WAYS TO TREAT COVID-19

Some of the drugs being developed to attack the disease and the SARS-CoV-2 virus that causes it

Block Viral Replication

DRUG	ACTION	COMPANY/LAB	STATUS
Remdesivir	Disrupt viral RNA synthesis	• U. of North Carolina • Vanderbilt University • Gilead Sciences	Clinical trials
EIDD-2801	Disrupt viral RNA synthesis	• Emory University • U. of North Carolina • Vanderbilt University • Ridgeback Biotherapeutics	Clinical trials
Danoprevir-Ritonavir	Inhibit viral protease enzyme	• Ascletis Pharma	Clinical trials
RNAi Experimental Compounds	Block viral RNA synthesis	• Alnylam Pharmaceuticals • Vir Biotechnology	Early research

Prevent Entry into Cells

DRUG	ACTION	COMPANY/LAB	STATUS
APN01	Decoy cell receptor	• Apeiron Biologics	Clinical trials
Multiple Human Antibody Cocktail	Antibodies neutralize virus	• Regeneron	Clinical trials planned for summer
Monoclonal Antibody Candidates	Antibodies neutralize virus	• Vir Biotechnology • Biogen • WuXi Biologics	Clinical trials planned
TAK-888	Modified antibodies against virus	• Takeda	Preclinical

Reduce Hyperimmune Response and Acute Respiratory Distress

DRUG	ACTION	COMPANY/LAB	STATUS
Kevzara (sarilumab)	Antibodies block IL-6 immune cell signal	• Regeneron • Sanofi	Clinical trials
Actemra (tocilizumab)	Antibodies block IL-6 immune cell signal	• Genentech • BARDA*	Clinical trials
Remestemcel-L	Stem cells modulate immune system	• Mesoblast NIH†	Clinical trials
Xeljanz (tofacitinib)	Inhibit inflammatory cells	• Pfizer	Clinical trials

*U.S. Biomedical Advanced Research and Development Authority
†National Institutes of Health

Conclusions

EIDD-2801, the compound with promising animal and test-tube results reported in early April, aims at the same viral enzyme. But unlike remdesivir, which much be given intravenously, EIDD-2801 can be taken as a pill. For this reason, Baric and other researchers investigating EIDD-2801, including George Painter, a professor of pharmacology and president of the Emory Institute for Drug Development, which first produced the drug, suspect it may end up being more widely used than remdesivir.[18]

In 2018 Painter and his colleagues identified EIDD-2801's activity during a search for a universal influenza medicine. When SARS-CoV-2 emerged, Painter's group immediately shifted focus. [17] EIDD-2801, like remdesivir, inhibits the coronavirus's self-copying operations, but it also works against virus variants with a mutation that made them resistant to the Gilead drug. In addition, EIDD-2801 is effective against a host of other RNA viruses, so it could serve as a multipurpose antiviral, much as some antibiotics can work against a wide variety of bacteria. For COVID-19, says Wayne Holman, co-founder of Miami-based Ridgeback Biotherapeutics, which has licensed the drug and is planning clinical trials, the goal is to have a pill that can be taken by patients at home early in the course of the disease to prevent it from progressing.[18]

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