COVID-19 treatment: *RNA polymerase inhibitors*

Coronavirus named for _____ on surface that create a

_____ in looking through electron microscope.

*RNA polymerase inhibitors → example of _____

A. Molnupiravir

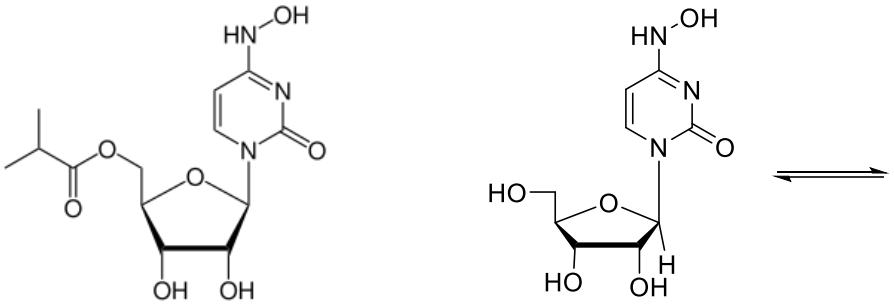
-oral anti-viral medication that _____

-considered a "_____" as it's converted to the active agent in vivo

-insertion in RNA genome causes _____

*originally developed at Emory University (G. R. Painter, G. R. Blueming, M. G. Natchus, D. Guthrie, 2018 Emory patent) → Ridgeback Therapeutics (Miami) → partnered with Merck & Co.

-approved in Nov. 2021 (UK); emergency use authorization by FDA in Dec. 2021



Summary of mechanism of action: *two _____→ one mimics _____,

one mimics _____

Cytidine:	Uridine:

*added to RNA instead of _____, but then _____

_____when copying RNA with molnupiravir

(actually _____ incorporates it)

_____ OR! _____

called "_____" or "_____"

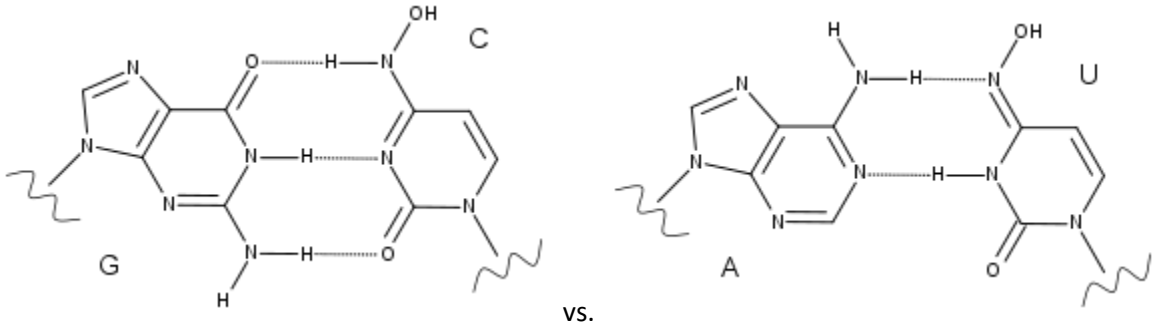
→ lots of mutations, lethal to species

see Nature Structural Biology 2021, 28, 740-6 C. Hobartner, P. Cramer et al.

https://www.nature.com/articles/s41594-021-00651-0

also Nature Structural Biology 2021, 28, 706-8

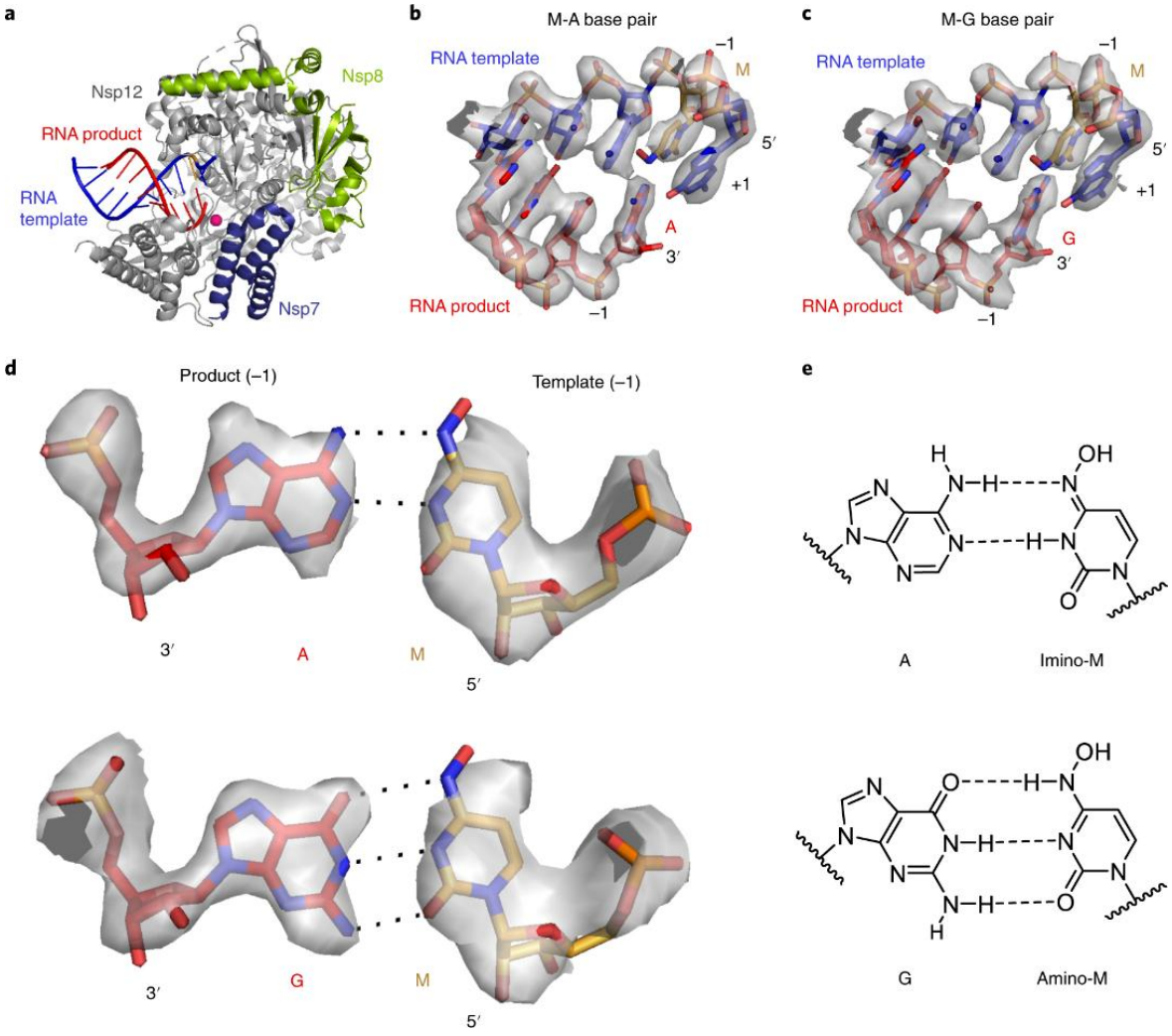
https://www.nature.com/articles/s41594-021-00657-8



vs.

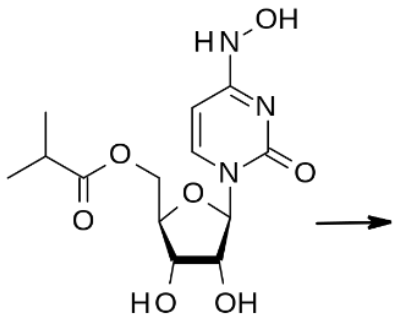
see Nature Structural Biology 2021, 28, 740-6 C. Hobartner, P. Cramer et al.

https://www.nature.com/articles/s41594-021-00651-0



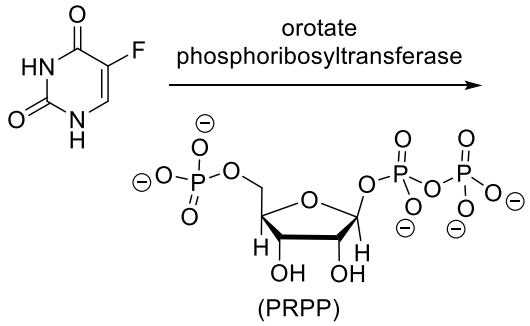
1. Mechanism of action:

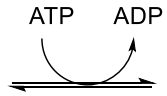
Converted in vivo to 5’-triphosphate:



Molnupiravir
EIDD-2801

(process shown in detail for 5-fluorouracil):

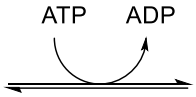




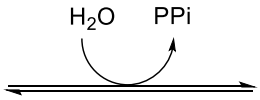
uridylate
monophosphate
(UMP) kinase

5-fluorouridylate

ribonucleoside
reductase



dUDP kinase

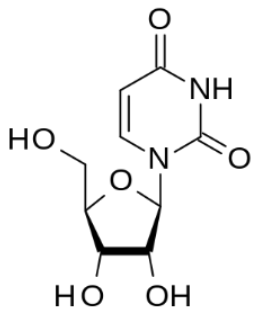


dUTP diphosphohydrolase

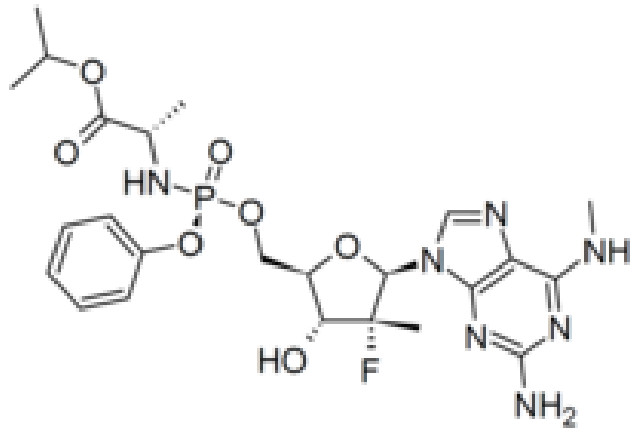
5-fluorouridine monophosphate
*active therapeutic agent!

2. Synthesis (from Wikipedia site)

*start with uridine and modify---quite simple



B. AT-527, a.k.a. Bemnifosbuvir



*_____ analogue

*irreversible _____ most common effect

-occurs after _____ added, a.k.a. "_____ chain terminator"

>>

Key review article of nucleotide drugs:

from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9773703/

"Kill or corrupt: Mechanisms of action and drug-resistance of nucleotide analogues against SARS-CoV-2" Ashleigh Shannon and Bruno Canard, Antiviral Res. 2023 Feb; 210: 105501.

>>

JBC 2020, 295, 6785 M. Gotte et al.

"AT-527, a Double Prodrug of a Guanosine Nucleotide Analog, Is a Potent Inhibitor of SARS-CoV-2 In Vitro and a Promising Oral Antiviral for Treatment of COVID-19", Steven S. Good et al. Antimicrobial Agents and Chemotherapy, 2021, e02479

https://journals.asm.org/doi/10.1128/AAC.02479-20 --> reports use with COVID-19

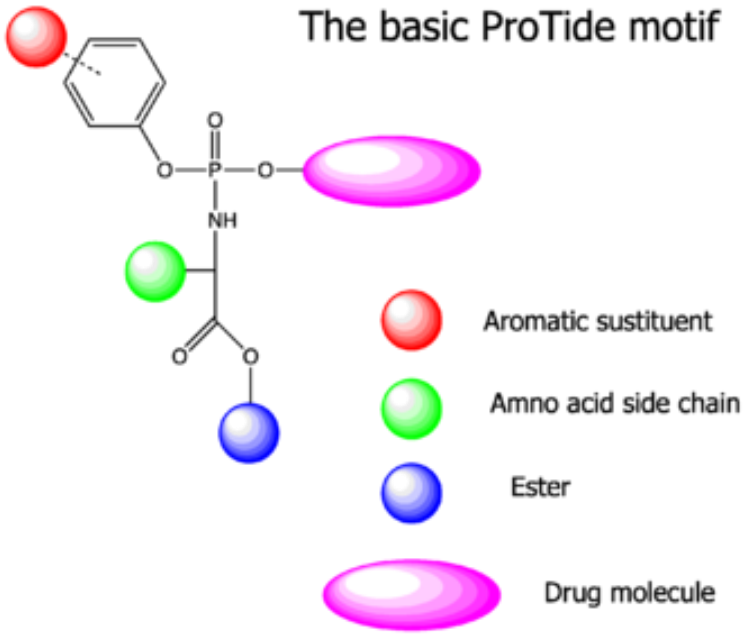
from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6879261/

Antimicrob Agents Chemother. 2019 Dec; 63(12): e01201-19.

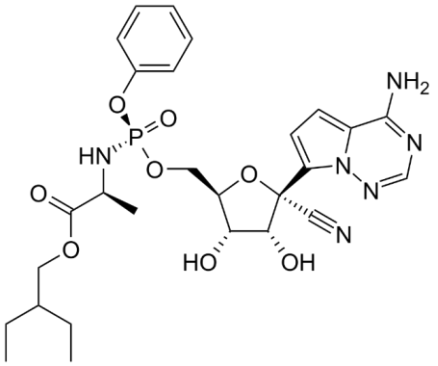
1. Bemnifosbuvir to activation

_____ technology: (from Wikipedia)

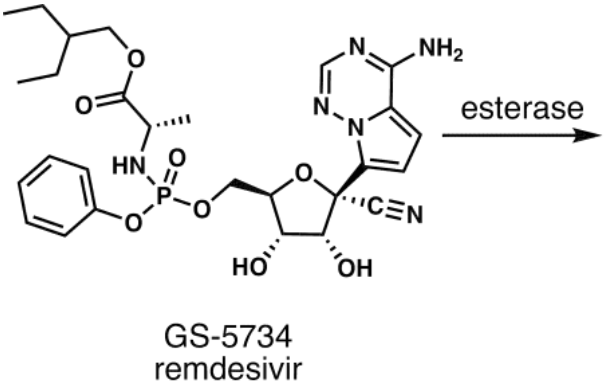
It was invented by Professor Chris McGuigan (School of Pharmacy and Pharmaceutical Sciences, Cardiff University) in the early 1990s. They form a critical part of the anti-viral drugs: sofosbuvir, tenofovir alafenamide and remdesivir.



Believed to be activated like _____ (Veklury, also a purine analog pro-drug and also used for COVID-19 treatment), for which the details are better understood.



(from Wikipedia, remdesivir)



GS-5734
remdesivir

Summary

-esterase is _____

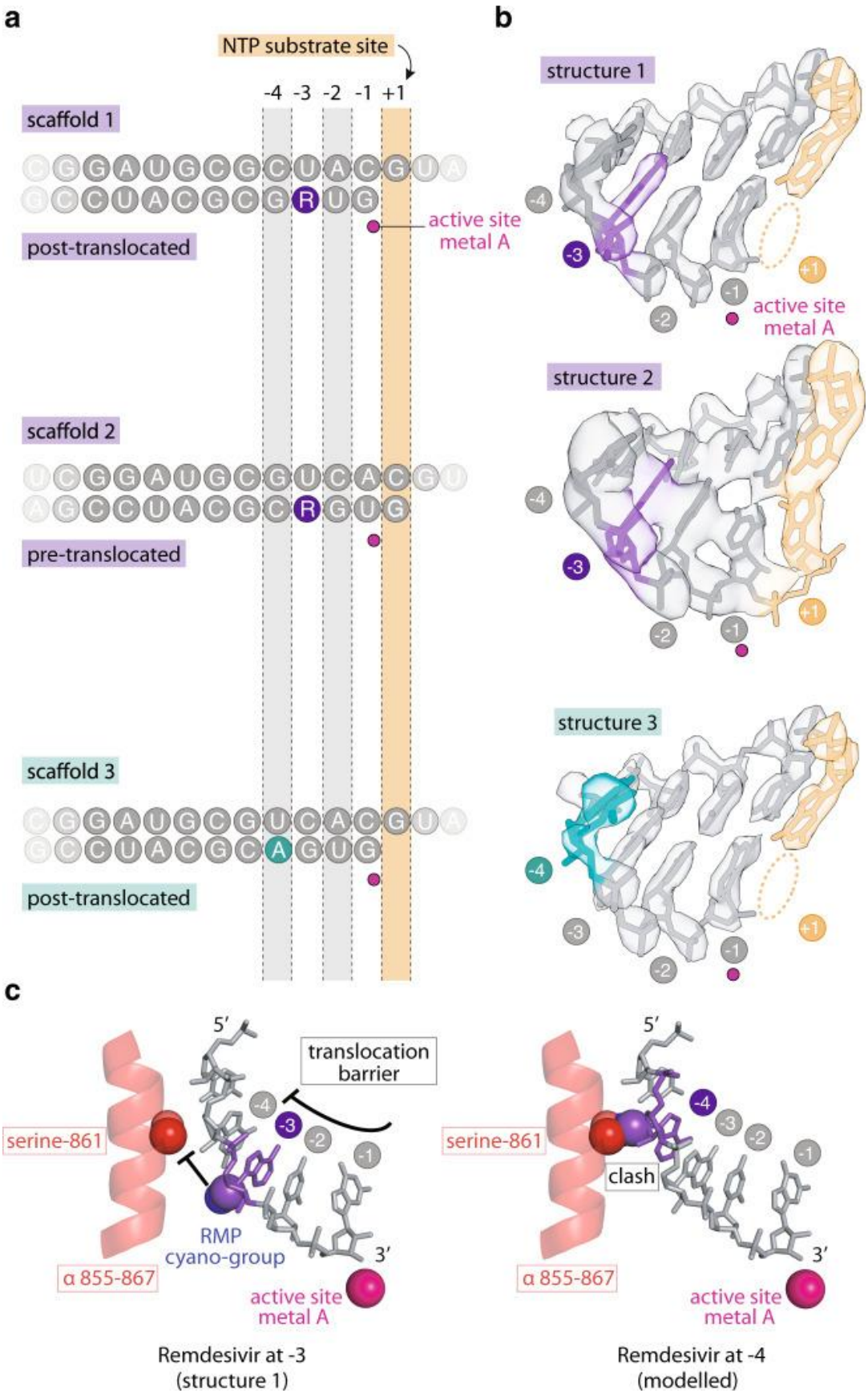
-_____ is histidine triad nucleotide-binding protein 1 (HINT1)

-_____ add two more phosphate groups

>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Excellent review article with complete review of related nucleic acid anti-virals: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9773703/

"Kill or corrupt: Mechanisms of action and drug-resistance of nucleotide analogues against SARS-CoV-2" Ashleigh Shannon and Bruno Canard, Antiviral Res. 2023 Feb; 210: 105501.


a
NTP substrate site
-4 -3 -2 -1 +1
scaffold 1
post-translocated
active site
metal A
scaffold 2
pre-translocated
scaffold 3
post-translocated
b
structure 1
active site
metal A
structure 2
structure 3
c
5′
translocation
barrier
serine-861
RMP
cyano-group
α 855-867
3′
active site
metal A
Remdesivir at -3
(structure 1)
clash
Remdesivir at -4
(modelled)

Structural analysis of remdesivir-induced RdRp stalling.

a Position of RNA scaffolds 1–3 as observed in RdRp-RNA complex structures 1–3. Template and product strands are on the top and bottom, respectively. b Cryo-EM density of RNA in the active center of structures 1–3. The active site metal ion was modeled41 and is shown as a magenta sphere. c The C1'-cyano group of the RMP ribose moiety (violet) is accommodated at position –3 (left), but would clash with the side chain of nsp12 residue serine-861 (red) at position –4 (right). Spheres indicate atomic van der Waals surfaces.