I make this report just to help people understand the aspect of the synthesis behind those 2 drugs. Don't take everything for the absolute truth because I can't be sure that they use this exact synthesis in the scale up process.

Remdesivir:

MW: 602.58 g/mol
Overall yield 2.2%

Gilead needs to synthesize 3 intermediates in order to make Remdesivir.

The 1st intermediate is the brominated amino base. It can be made from commercially available precursors (depicted in the following scheme). The overall yield for this sequence is 22.67% according to the literature.

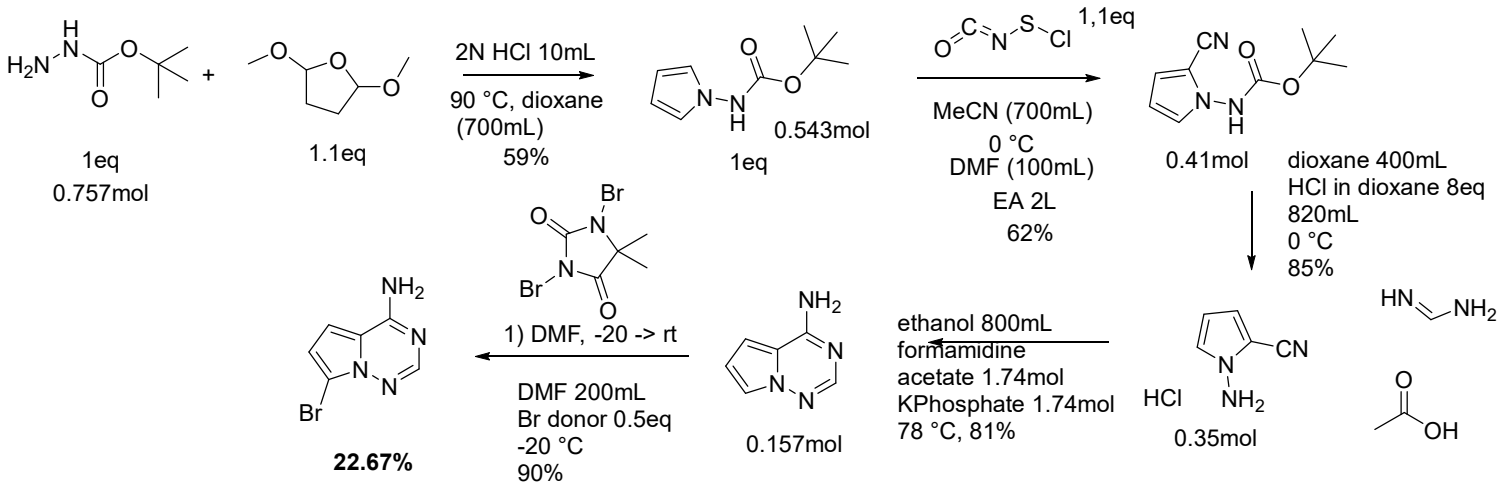

Figure 1 : amino base synthesis (piece 1)

Then, you need the following lactone which can be made in 4 steps with 72.3% yield from the common D-ribose.

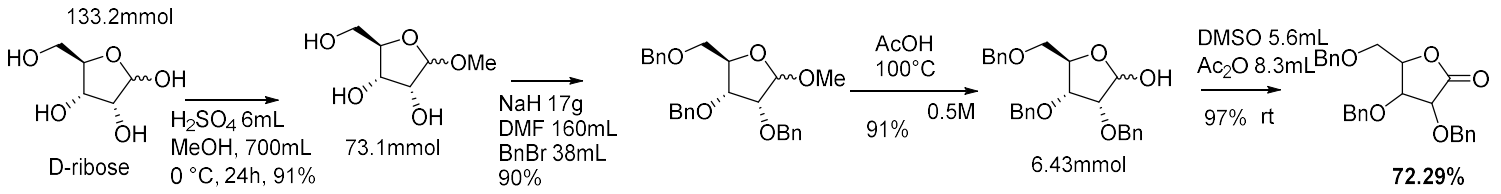

Figure 2 : lactone synthesis (piece 2)

Finally, the phosphonate synthesis is made in 2 steps from alanine and this primary alcohol in 35.5%.

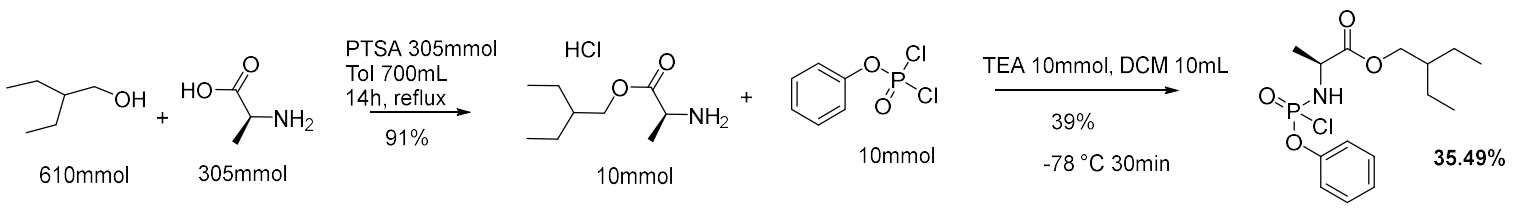

Figure 3 : Phosphate synthesis (piece 3)

Once all pieces have been synthesized, you need to assemble the jigsaw puzzle. The amino base undergo bromo lithium exchange thanks to butyl-lithium in THF and is added to the previously synthesized lactone. A mixture of diastereoisomers is observed. Addition of cyanide anion via SN1 mechanism allow the formation of this nucleoside (mixture of diastereoisomers). Finally, submitting this product to the Lewis acid Boron Trichloride yields the deprotected nucleoside in 7.46% from the beginning of the synthesis. This compound is purified via reverse phase HPLC in order to separate both diastereoisomers.

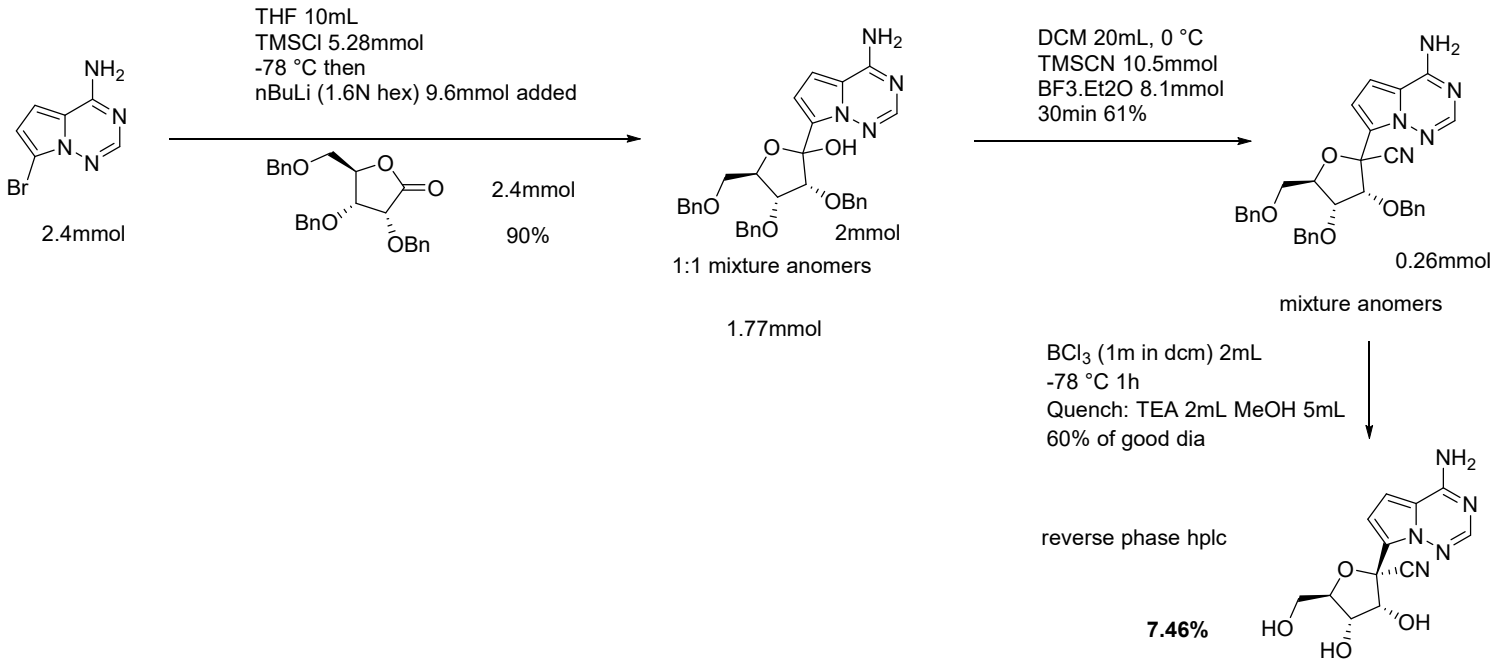

Figure 4 : Nucleoside synthesis

At this stage of the synthesis, the last thing to be done is the coupling between this nucleoside and the phosphate partner in order to obtain the nucleotide Remdesivir. One of the big disadvantage here, is the formation of a new stereocentre on the phosphorus. This means that over 59% yield, only half of it basically gives the finale product. Moreover, a chiral resolution on a big scale must be a pain in the ass.

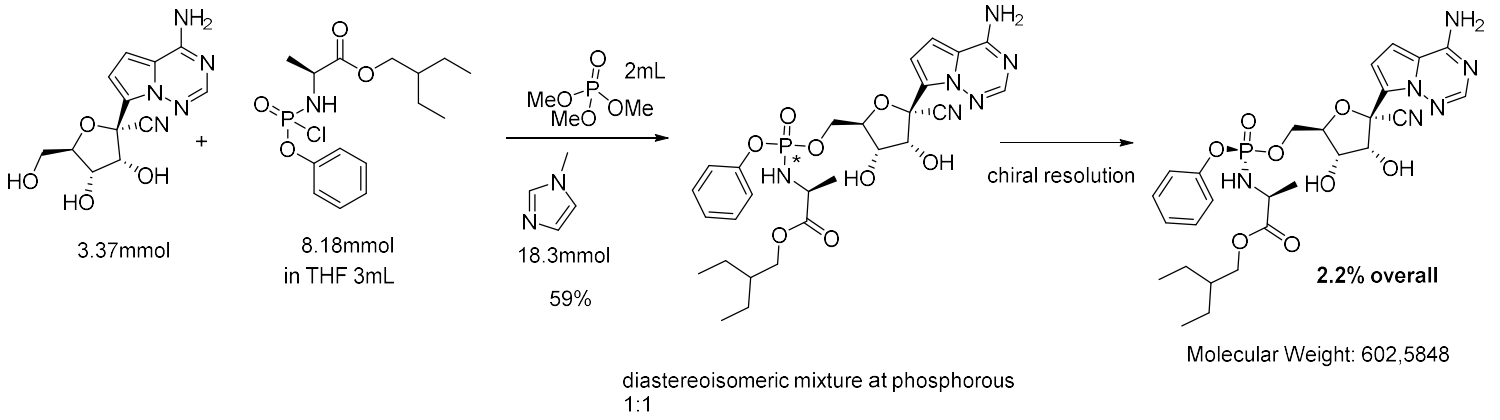

Figure 5 : Remdesivir synthesis

Remdisivir has a total of 15 steps. The big disadvantage are the selectivity issues which decrease the overall yield a lot. Stereoselectivity has always been an issue in organic synthesis and this is why so many research groups focus their work on improving such reactions. This will be made possible via catalytic process but it is not usable in industry due to the high cost of those catalysts.

Galidesivir:

MW=265.27 g/mol
Overall yield: 6.61%

Galidesivir synthesis follows the same principle that Remdesivir's. Indeed several pieces have to be made in order to make the finale drug. Galidesivir is actually synthesized through a well-known intermediate Immucilin F (also known as BCX-1777).

Commercially available Gulonolactone allows the formation of the imine in 10 steps. Although this could seem like a lot of steps, the overall yield is very decent (22.5%). Moreover, this sequence has been designed in the late 80's and is well-established and used in process scale synthesis. It means that, this sequence can be done on multigram/kilogram scale without any doubts and any problems.

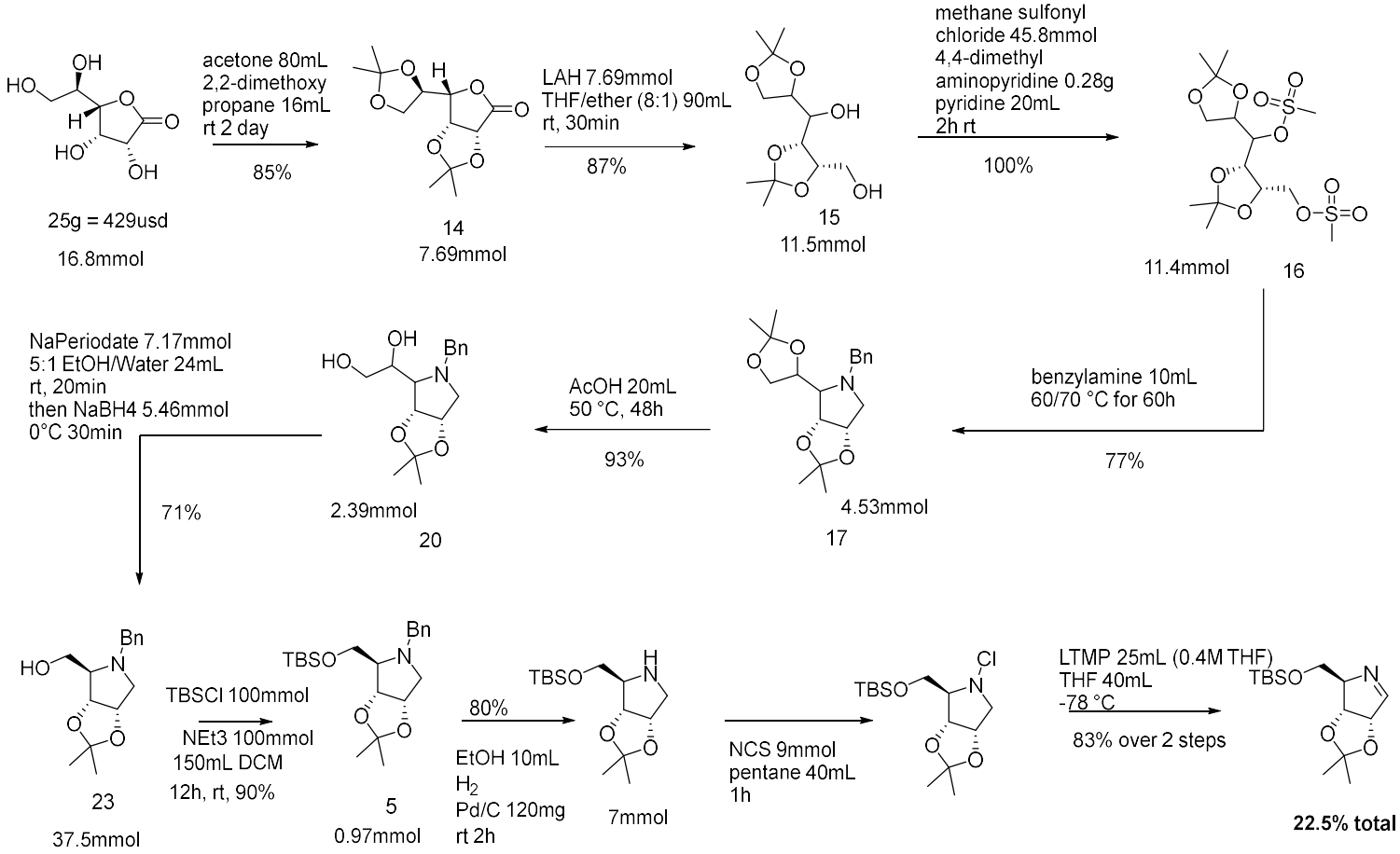

Figure 6 : synthesis of imine (piece 1)

The second objective is to form the nucleoside. To do so, the desired aminobase is synthesized in 2 steps from the chloride derivative. With this newly-formed compound in hand, we can couple the imine (previously synthesized) together with this aminobase. Then, acetonide, TBS and CH2OBn deprotection yield Immucilin F in 15.56% from the beginning. As you probably noticed, no selectivity issues are observed during the addition of the nucleobase onto the imine. We don't suffer diastereoselectivity problems! This is partly due to the conformation of the cyclic imine and the acetonide group which blocks one face of the molecule making the attack less feasible.

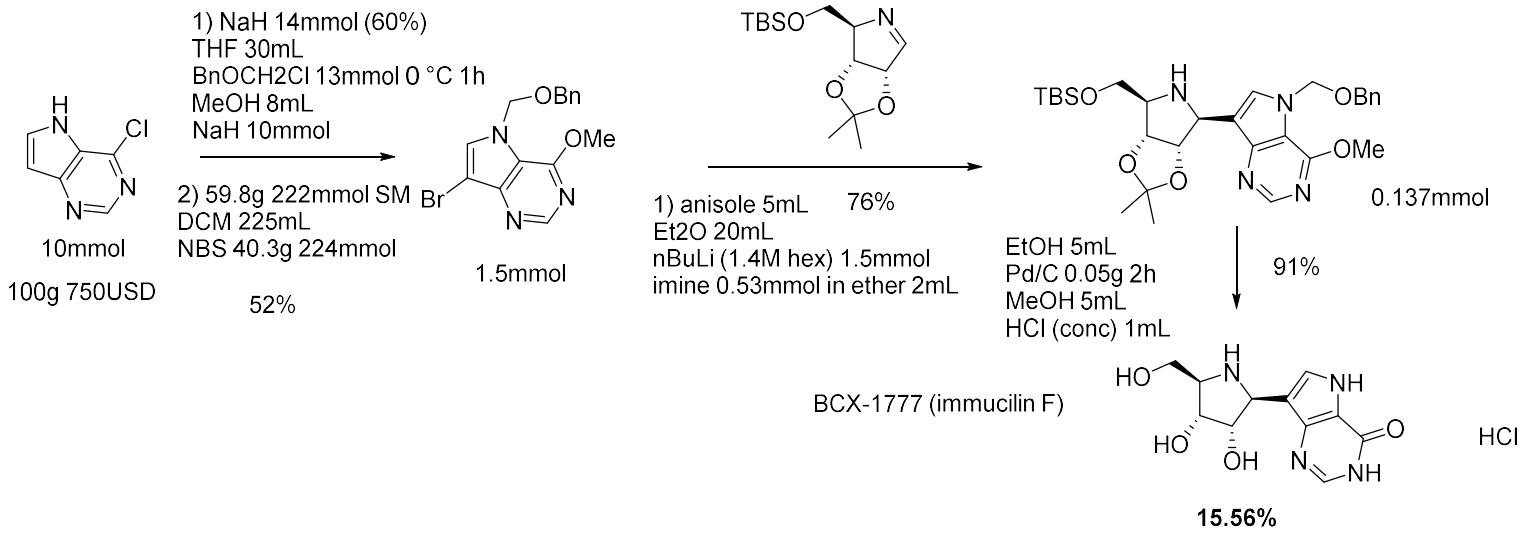

Figure 7 : synthesis of the intermediate Immucilin F

The last 7 steps depicted below have an overall yield of 42.5% which gives an overall yield of 6.61% for the synthesis of Galidesivir. All those steps are really straightforward. The 2 first steps are just simple protection. The 2 last one are deprotection steps. The third step only lasts 10 minutes. Overall those last 7 steps are really not hard to scale up. Indeed, the patents were I've been taking those information gives example were the synthesized about 100g of Galidesivir.

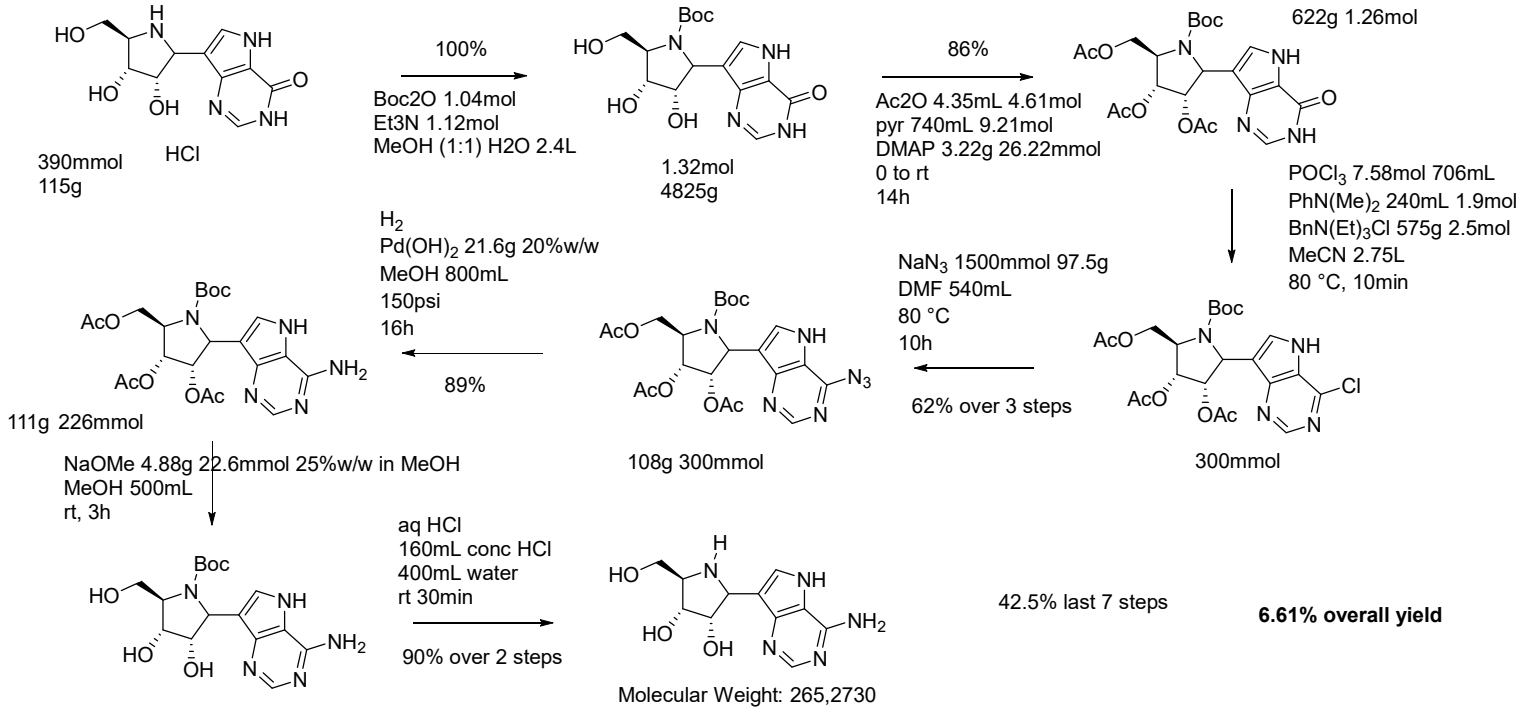

Figure 8 : last sequence to obtain Galidesivir

Galidesivir has a total of 21 steps.

Conclusion:

Even though you need more steps to synthesize Galidesivir, the overall yield is way better. It is important to notice that the molecular weight of Remdesivir is way about 3 times bigger than the one of Galidesivir. This means that the synthesis of 1kg of Remdesivir represents 1.66 mol whereas it represents 3.77 mol for Galidesivir.

The mole represents the number of molecule! The more you have the better, because you need one molecule per cells (infected by the virus) to kill the virus. I guess what I'm saying is a pill of 200mg of Galidesivir contains about 2.5 times more molecule than 200mg of Remdesivir!

Remdesivir requires 7 steps at temperature below or equal to 0 °C. It's obviously not a big deal, but will cost more energy and time (might need to decrease the size of the batch).

Regarding Galidesivir, it requires 4 steps at temperature below or equal to 0 °C.

Once again, it is important to note that, this data could be inaccurate. Maybe, Gilead and BCRX don't need to start as early as I expect in terms of precursors. They might have some labs who synthesis hundreds of kilograms of each intermediate they need and then take care of the coupling by themselves.

I hope this will give you some ideas about the way those drugs are made.

I didn't have time to go through the price estimation of every synthesis for several reasons:

1) It would be completely inaccurate because I have 0 clue how much they pay for their chemicals (you can check 100 chemical suppliers which will give you 100 different prices for each chemical)
2) It would be too big of a burden to me to do so (about 20h of work) and I don't think it would bring too much as an investment consideration.

The synthetic part of a drug can be a pain in the ass but they will make it anyway. Look at eribulin made by Eisai, it has a linear sequence of 59 steps LOL! It still is commercialized and synthesized that way even though my lab developed an 18-step synthesis… it would be too complicated for them to change their process now.

I think that the result of the clinical trials will be crucial and will tell us a lot about what we can expect from Galidesivir.

If you have any questions, concerns or remarks let me know and I'll try to answer the best as I can!