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Cellular activation pathway of Bemnifosbuvir (AT-527), a drug-candidate against SARS-CoV-2 infections

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The current pandemic of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has caused substantial health issues and emphasizes the immediate need of powerful antivirals. Nucleoside/tide analogues have proved their efficiency as polymerase inhibitors against many viruses [1] and hold a place of choice in the fight against coronaviruses. [2] Bemnifosbuvir (AT-527), a phosphoramidate nucleotide analogue prodrug, recently entered phase III clinical trials for the treatment of COVID-19. Once in cells, AT-527 is converted into its triphosphate form, AT-9010, that targets the nsp12 gene product at both its viral RNA-dependent RNA polymerase and nucleotidyltransferase activity, accounting for its antiviral effect. [3]

Because the conversion of a prodrug into its active form is crucial for its final antiviral efficiency, we aim to provide a better understanding, on biochemical and structural levels, of the key enzymes dictating the metabolic activation pathway of AT-527.

Here, we have identified five enzymes allowing the activation of AT-527 into its active principle AT-9010 (Fig. 1). These five enzymes reconstituting the metabolic pathway were expressed, purified, and shown to catalyse qualitatively and quantitatively reactions on their respective metabolites, in an ordered pathway. To go further in understanding, the specificity of some key enzymes together with crystallographic structures of enzyme/substrate co-complexes were studied to open to new possibilities to design improved nucleotide analogues which are most relevant to targeted cellular, tissues, and animal models.

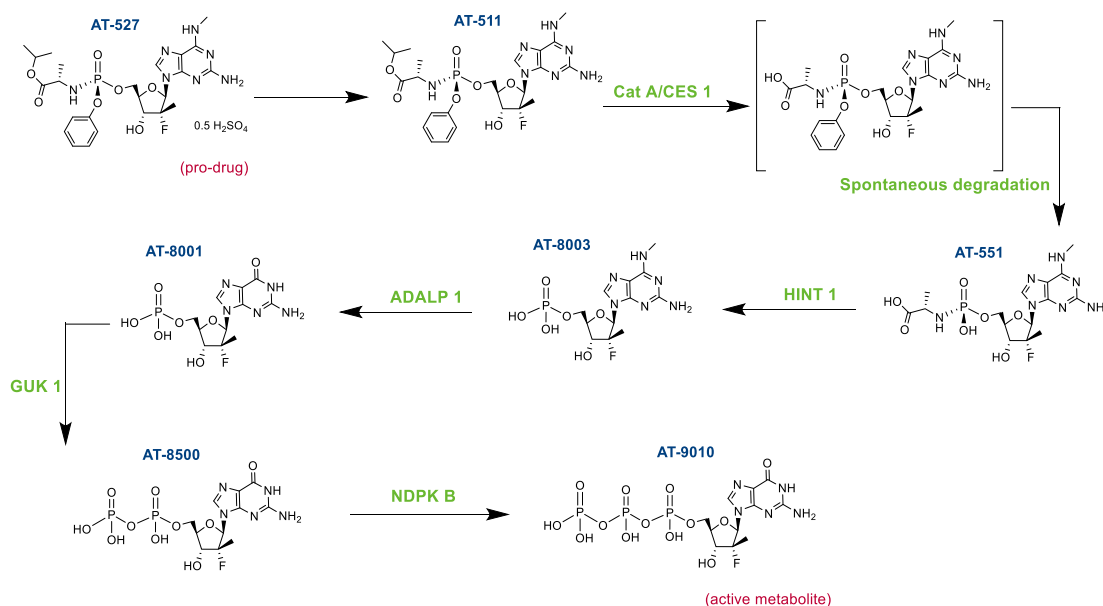


Figure 1. Proposed metabolic pathway of Bemnifosbuvir (AT-527), adapted from Good *et al.*, 2020 [4]

[1] De Clercq, E. (2012). *Acta Pharmaceutica Sinica B*, **2**, 535–548.

[2] Pruijssers, A. J. & Denison, M. R. (2019). *Current Opinion in Virology*, **35**, 57-62

[3] Shannon, A., Fattorini, V., Sama, B., Selisko, B., Feracci, M., Falcou, C., Gauffre, P., El Kazzi, P., Delpal, A., Decroly, E., Alvarez, K., Eydoux, C., Guillemot, J.C., Moussa, A., Good, S., La Colla, P., Lin, K., Sommadossi, J.P., Zhu, Y., Yan, X., Shi, H., Ferron, F & Canard, B., (2022). *Nature Communications*, **13**, 621

[4] Good, S., Moussa, A., Zhou, X.J., Pietropaolo, K., J.P., Sommadossi., (2020). *PLOS ONE*, **15**, e0227104