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Molecular Hybridization of Repurposed Drugs to Develop MTDLs against SARS-Cov-2

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Letter to Editor

Coronaviruses (CoVs) is a group of +RNA viruses which are capable to infect a wide range of vertebrates including humans and are the causative agents of severe acute respiratory syndrome (SARS) and various other respiratory infections [1]. CoV-19 belongs to beta type of corona virus family. Beta corona virus genome encodes several proteins which include glycosylated spike protein (S), angiotensin-converting enzyme 2 (ACE2) and nonstructural proteins including RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro) [2-4]. All the proteins have significant roles throughout the viral progression cycle [5]. RdRp is an enzyme which is responsible for the replication of viral RNA from an RNA template [6]. Due to its central role in replication of virus, RdRp is a significant and attractive target for the drug development and design against SARS-CoV-2 infections [7-8]. Several antiviral drugs are already available against RdRp and Galidesivir is one among them.

Drug repurposing is a technique for utilization of therapeutic value of an existing drug by focusing on infections other than that for which it was initially proposed [9]. Repurposing of already approved therapeutic drugs towards new activity is an attractive approach to the researchers, medicinal chemists, clinicians, drug developers and public health organisations according to the need of the hour [10].The concept of multi-target directed ligands (MTDLs) offers construction of such molecules which are able to bind to multiple targets. MTDLs are of utmost importance and in the past few years there is continuous research is in progress in this direction [11-14]. Therefore construction of hybrid molecules by combining two or more scaffolds/compounds in a single molecule is a suitable strategy in the development of MTDLs. In Figure 1, we have proposed a strategy to develop such kind of MTDLs against Covid-19.

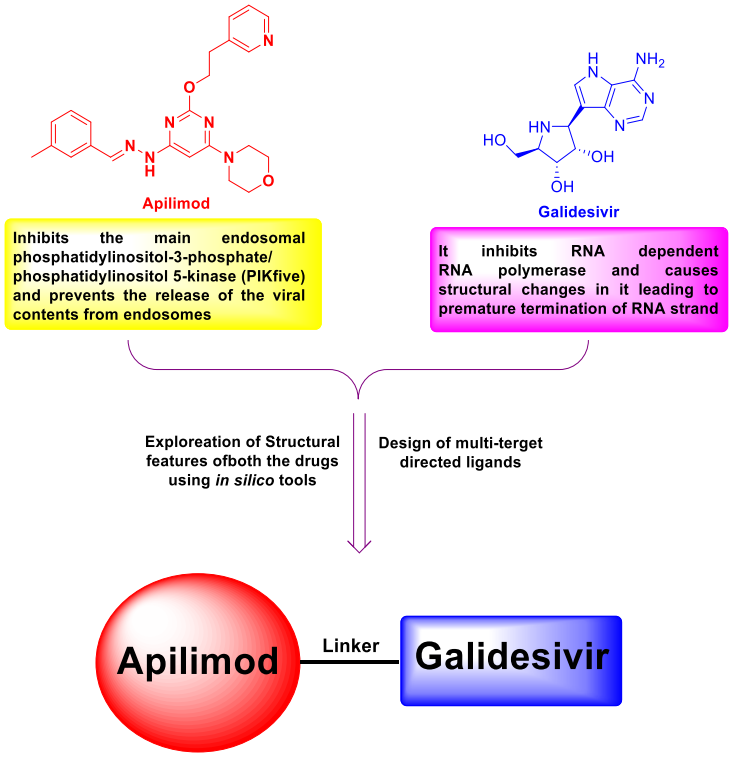

Figure 1: *Strategy to develop MTDLs against SARS-CoV-2.*

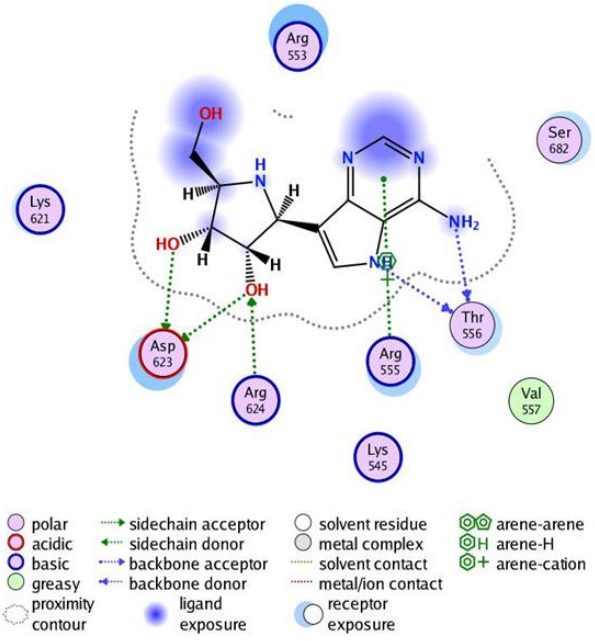

Figure 2: *Interactions of Galidesivir against RdRp.*

In this strategy we have proposed hybridization of Apilimod with Galidesivir through a suitable linker. Apilimod is a well-established endosomal phosphatidylinositol-3-phosphate/phosphatidylinositol 5-kinase inhibitor and prevents release of viral contents from endosomes. On the other hands Galidesivir is a potent inhibitor of RNA dependent RNA polymerase and interferes with genome replication of virus. Hence combination of two moieties in a single molecule may target both the targets at the same time. Drug developer can get an idea from this strategy and they can hybridize some other drugs instead of these two mentioned here (Figure 1,2).

Figure 2 represents some interactions of repurposed drug Galidesivir with RdRp protein which was obtained from docking studies against it using MOE software. It shows significant interactions with Asp623 (H bond with OH at a distance 1.90A), Asp623 (H bond with OH at a distance 2.04A), Arg624 (H bond with OH at a distance 2.26A), Arg555 (Arene-cation with Pyrimidine), Thr556 (H bond with NH at a distance 1.97A), Thr556 (H bond with NH at a distance 1.98A) [15,16]. Therefore medicinal chemists, drug developers, clinicians should work towards this direction by combining the concepts of drug repurposing and molecular hybridization to design and synthesize newer hybrid molecules as a therapy against SARS-CoV-2.

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