Drug Repurposing: Dipeptidyl Peptidase IV (DPP4) Inhibitors as Potential Agents to treat SARS-CoV-2 (2019-nCov) Infection

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- **Abstract:** The current outbreak of severe acute respiratory distress syndrome (SARS) or nCOVID-19 pandemic, caused by the coronavirus-2 (CoV-2), continues to wreak havoc globally. Unfortunately, there are no concrete treatment options available which has severely hampered the pharmacotherapy of this devastating infection. This calls for an urgent need to consider alternative strategies which can be employed quickly, as discovering new drugs for SARS-CoV-2 infections is a time consuming and expensive proposition. In this regard, **drug repurposing** is an appealing approach which can provide rapid access to therapeutics with proven record of safety and efficacy. Accordingly, we investigated the drug repurposing potential of a library of **dipeptidyl peptidase 4 (DPP4) inhibitors** which are currently marketed for type-2 diabetes, to treat SARS-CoV-2 infections. Computational studies were conducted in the crystal structure of the substrate binding site of viral protease, the *SARS-CoV-2 M^{pro} dimer*, which led to the identification of three marketed DPP4 inhibitors; gemigliptin, linagliptin and evogliptin exhibiting favorable binding, in the *SARS-CoV-2 M^{pro} dimer*, viral protease. These studies supports further investigation of repurposing DPP4 class of inhibitors and their potential in treating SARS-CoV-2 infections, especially in elderly patients with type-2 diabetes, who are at a greater risk of suffering from increased disease severity and mortality.

- **Keywords:** Cysteine proteases, dipeptidyl peptidase IV inhibitors, drug repurposing, molecular docking,SARS-CoV-2 infection, SARS-CoV-2 M^{pro} dimer, type-2 diabetes

- **Background:** Discovering novel drugs and bringing them to the market is a time consuming, expensive and risky process. In this regard, drug repurposing or the application of known marketed drugs, to treat novel diseases such as the current SARS- CoV-2 pandemic, is a practical approach that should be thoroughly investigated. Successful drug repurposing can identify safe and effective drugs to treat diseases in a short time span instead of the need to spend 10-15 years that is typically required to discover and develop new drugs. Drug repurposing approach provides billions of dollars in cost savings and can also dramatically reduce the time required to launch new drugs. Recently, Zhang and coworkers made seminal breakthrough in COVID-19 research by solving the crystal structure of SARS-CoV-2 viral protease, also called as main protease M^{pro} or 3CL^{pro} with a peptidomimetic α-ketoamide inhibitor (*tert*-butyl 1-((2*S*)-1-((2*S*)-4-(benzylamino)-3,4-dioxo-1-(2-oxopyrrolidin-3-yl)butan-2-ylamino)-3-cyclopropyl-1-oxopropan-2-yl)-2-oxo-1,2-dihydropyridin-3-ylcarbamate **1**, Fig. 1, *Science*, 368, 409-412, 2020). We conducted systematic *in silico* investigation of FDA/market approved DPP4 inhibitors; a library of 12 DPP4 inhibitors or gliptins – vildagliptin, saxagliptin, anagliptin, alogliptin, trelagliptin, sitagliptin, linagliptin, gemigliptin, tenegliptin, omarigliptin, evogliptin and gosogliptin (Fig. 1) using the crystal structure of SARS-CoV-2 M^{pro} viral protease, by conducting molecular docking studies, pharmacophore modeling and by analyzing their molecular properties with the known SARS-CoV-2 viral protease inhibitor **1** (Fig. 1).

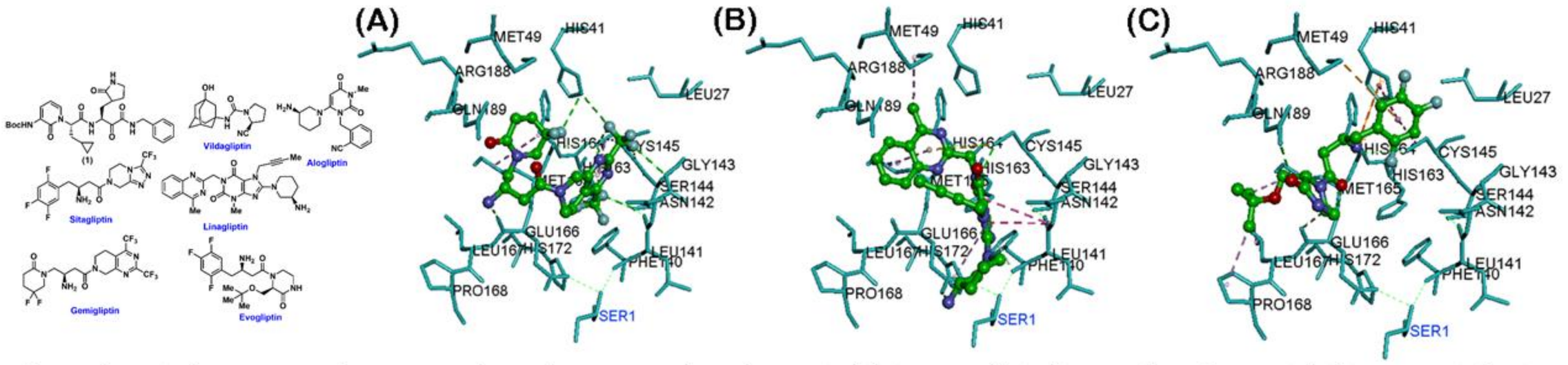

Fig 1: Chemical structure of compound 1 and some marketed DPP4 inhibitors and binding modes of DPP4 inhibitors gemigliptin (A), linagliptin (B) and evogliptin (C) in the SARS-CoV-2 M^{pro} dimer (PDB ID: 6Y2G). Hydrogen atoms are not shown to enhance clarity

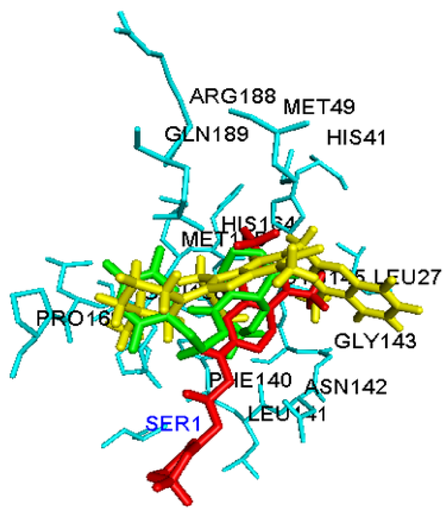

Fig 2: Binding modes of DPP4 inhibitors gemigliptin (red stick cartoon), linagliptin (yellow stick cartoon) and evogliptin (green stick cartoon) in the SARS-CoV M^{pro} dimer (PDB ID: 1UK4). Hydrogen atoms are not shown to enhance clarity.

Table 1: CDOCKER Energy and CDOCKER Interaction Energy data for DPP4 inhibitors in the SARS-CoV-2 M^{pro} protomer

Compound Name	CDOCKER Energy in kcal/mol	CDOCKER Interaction Energy in kcal/mol
Linagliptin	–34.15	–50.46
Gemigliptin	–39.55	–48.54
Evogliptin	–33.95	–39.96
1	–56.14	–70.00

The CDOCKER energy and CDOCKER interaction energies for the top ranked binding poses of DPP4 inhibitors obtained after conducting the molecular docking studies on the SARS-CoV-2 M^{pro} protomer (PDB ID: 6Y2F using the CDOCKER algorithm in the software *Discovery Studio Structure-Based-Design,* BIOVIA Inc)

Results: Our *in silico* studies identified three DPP4 inhibitors gemigliptin, linagliptin and evogliptin that have the potential to interact and bind to SARS-CoV-2 M^{pro} viral protease. Furthermore, our molecular docking studies show that DPP4 class of drugs can undergo favorable interactions both with the inactive viral protease (SARS-CoV-2 M^{pro} protomer, Table 1) and the catalytically active dimer (SARS-CoV-2 M^{pro} dimer, Fig 1 & 2, Table 1), suggesting their potential to inhibit SARS-CoV-2 viral replication.

Conclusions: Our computational studies highlight the potential of DPP4 class of drugs in inhibiting SARS-CoV-2 viral protease. The increased risk of type-2 diabetic patients to SARS-CoV-2 infection, suggests that DPP4 class of drugs have the potential to be repurposed in treating SARS-CoV-2 infection.

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