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Research Article

COMPUTATIONAL SCREENING OF FOLATE ANALOGUES AGAINST THE SARS-COV-2 CORONA VIRUS BY MOLECULAR DOCKING

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ABSTRACT

The outbreak of corona virus disease 2019 (COVID-19) has created a global health crisis that has had a deep impact on the way we perceive our world and our everyday lives. To date, there are no specific vaccines or medicines for COVID-19. COVID-19 virus main protease plays a vital role in mediating viral transcription and replication. In the present study, folic acid and its analogues (Folate(2-), Pemetrexed, 10-Formyl Folic Acid, Pralatrexate, Pteroyltriglutamic acid, Pentaglutamyl folate) were screened against COVID-19 virus main protease using Autodock Vina. Interaction between amino acid of targeted protein and ligands was visualized by Dicovery studio. Docking studies revealed that the folate analogues compounds showed promising inhibiting activity of Covid-19 main protease M^{pro} with significant binding energy.

Keywords: Coronavirus , SARS-CoV-2 , COVID-19 , Molecular docking, Folic Acid Analogs

1. INTRODUCTION

COVID-19, a member of corona virus family is spreading its tentacles across the world due to lack of drugs at present. Corona viruses are enveloped, (+) single stranded RNA viruses with a crown like appearance, belongs to the family Coronaviridae, order Nidovirales which is further divided into four genera (α, β, γ and δ), subgenera Sarbecovirus, species is SARS CoV [1]. Four CoVs commonly found among humans are HCoV2–229E, -HKU1, -OC43 and -NL63. Novel CoV–2 is a zoonotic form of the beta-corona virus which can rapidly mutate and recombine although mutations are natural part of the virus life cycle [2, 3]. Drug development against corona virus includes inhibition of viral replication through acting on its critical enzymes. The SARS-CoV-2 genome encodes several structural proteins such as the glycosylated spike protein, envelop protein, membrane protein, ucleocapsid protein. In addition, the viral genome also encodes numerous nonstructural proteins, including RNA-dependant RNA polymerase (RdRp), coronavirus main protease (CoV M^{pro}) and papaine-like protease (PL^{pro}). Upon entrance to the host cell, the viral genome is released and subsequently translated into viral polyproteins using host cell translation machinery, which are cleaved into effector proteins by viral proteases PL^{pro} and CoV M^{pro} [4, 5]. CoV M^{pro} protease plays a critical role in the virus replication process. Therefore, it is a potential target for anti corona virus screening [6].

Folate is a B group vitamin and is widely distributed in nature. Folate is vital for several biochemical pathways such as acting as essential donors and acceptors of one-carbon transfer reactions [7]. Folate is also involved in the methylation and DNA biosynthesis cycle in almost all organisms [8]. Folate species are composed of a pteridine ring, p-aminobenzoate and linked to polyglutamyl chains. Folate species are differentiated by the reduction state of the pteridine ring (tetra- or dihydro- folate), one-carbon substituent at the N 5 and/or N 10 positions, and the length of the μ-glutamyl chains [9].

Folic acid is a water-soluable vitamin belonging to the B-complex group of vitamins. Folic acid is also known as folate, or folacin. Folic acid is found in leafy green vegetables, beans, peas and lentils, liver, beets, brussel sprouts, poultry, nutritional yeast, tuna, wheat germ, mushrooms, oranges, asparagus, broccoli, spinach, bananas, strawberries, and cantaloupes. Folic acid works together with vitamin B12 and vitamin C to metabolize protein in the body. It is important for the formation of red and white blood cells. It is necessary for the proper

differentiation and growth of cells and for the development of the fetus. It is also used to form the nucleic acid of DNA and RNA. It increases the appetite and stimulates the production of stomach acid for digestion and it aids in maintaining a healthy liver. A deficiency of folic acid may lead to anemia, in which there is decreased production of red blood cells. This reduces the amounts of oxygen and nutrients that are able to get to the tissues.

Folate(2-) is the dicarboxylic acid dianion formed from folic acid by loss of a proton from each of the two carboxy groups in the glutamic acid moiety. It has a role as a Saccharomyces cerevisiae metabolite. It is a dicarboxylic acid dianion and a member of folates. It is a conjugate base of a folic acid.

Pemetrexed is chemically similar to folic acid and is in the class of chemotherapy drugs called folate antimetabolites. Pemetrexed belongs to a new generation of multitargeted antifolate cytotoxic agents. It was first approved in 2004 by the U.S. Food and Drug Administration in combination with cisplatin for nonresectable pleural mesotheliomas. Pemetrexed has demonstrated clinical activity in non-small cell lung cancer as well as in a broad array of other solid tumors, including mesothelioma, breast, colorectal, bladder, cervical, gastric and pancreatic cancer [10].

Pteroyltriglutamic acid (Pteropterin) is a crystalline conjugate of folic acid containing three molecules of glutamic acid instead of one and having the general properties of a polypeptide. Pralatrexate (Folotyn) is a folate analogue metabolic inhibitor that was used for the treatment of relapsed or refractory Peripheral T-cell lymphomas. It is more efficiently retained in cancer cells. It is the first drug approved as a treatment for patients with relapsed or refractory peripheral T-cell lymphoma [11]. Pentaglutamyl folate is a naturally occurring form of folic acid. 10-Formyl Folic Acid is a Folic acid derivative found in daily dietary intake that is often used in cancer risk correlation studies.

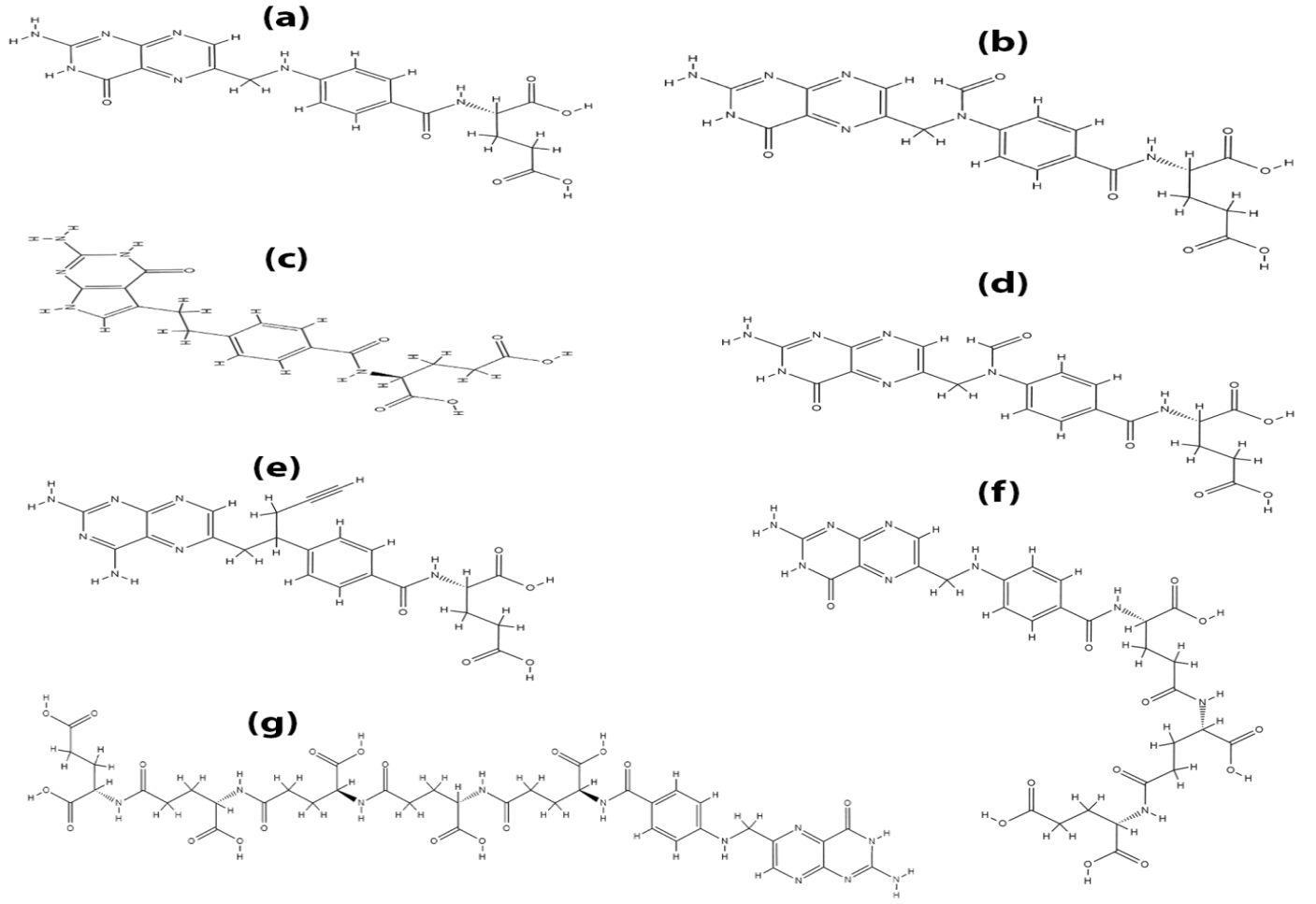

Fig. 1: Structure of Folate analogues compounds. (a) Folic Acid, (b) Folate (2-), (c) Pemetrexed, (d) 10-Formyl Folic Acid, (e) Pralatrexate, (f) Pteroyltriglutamic acid, (g) Pentaglutamyl folate

2. MATERIAL AND METHODS

Three-dimensional structure file (PDB code: 6LU7) of the SARS-CoV-2 Mpro was downloaded from the RCSB PDB database [12] and prepared in AutoDock Tools [13]. The water, solvent molecules and the bound ligand was removed. Polar hydrogen and partial charges are added. These all processes were carried out in the Auto Dock window execution file. The prepared structure was saved in AutoDock PDBQT format.

The investigation ligand was downloaded from Nation Library of Medicine-PubChem as sdf file and optimized for energy minimization using MM2 force field. Open Bablel was used to convert pdb file into pdbqt file format.

In the current study, identification of binding modes of the folate analogues compounds target was identified using AutoDock Vina software program. Moreover, to confirm actual binding interaction with targets blind docking was performed and the best conformers were represented with lowest binding energy (-kcal/mol) which pave the way to disclose the mode of actions of these ligands. The docking parameters were defined as coordinates of the center of binding site with x =126, y =126, z = 126 and binding radius = 0.531Å. Conformers of the ligand were automatically docked to the enzymes and most stable conformer in terms of binding affinity (most negative) was used for post-docking analysis. The results of the virtual screening experiment were ranked according to the binding energy of their best scoring conformation. The top ranked candidates were selected for further analysis. Visual investigation of docking poses and the analysis of protein ligand interactions were performed in Pymol and Discovery studio.

3. RESULTS AND DISCUSSION

The main protease enzyme M^{pro} is a chymotrypsin-like cysteine protease plays the prime role in mediating the replication and transcription of virus and hence this enzyme has been key target for finding of antiviral agents. The existence of the corona virus M^{pro} was first predicted by sequence analysis of IBV replicase polyprotein in 1989 [14]. The inhibition potential of ligand depends upon the active sites of molecules and structure of ligands.

Our study revealed that Pteroyltriglutamic acid, Folic acid, Pentaglutamyl folate and Folate(2-) docked against Covid-19 main protease M^{pro} showed maximum binding with binding energies -8.3 kcal/mole, -8.2 kcal/mole, -8.2 kcal/mole and -8.1 kcal/mole, respectively. The results of docking studies are given in the Table1.

Pteroyltriglutamic acid was most effective compound against against Covid-19 main protease $M^{pro.}$ Molecular docking of Pteroyltriglutamic acid with the target molecule is shown Fig.2.

Table 1: Ligand binding energy and Binding site

Sl No	Ligand	Binding Energy (kcal/mol)	Binding site
1	Folic acid	-8.2	ASN 119, THR 26, GLY 143, SER 144, LEU 141, CYS145
2	Folate(2-)	-8.1	ASN 142, GLA 189, GLN 192, GLU 166, HIS 163, PHE 140, THR 190
3	Pemetrexed	-7.3	ARG 131, ASP 197, LYS 137, THR 199
4	Pentaglutamyl folate	-8.2	MET 165, GLN 192, GLU 166, GLY 143, LEU 167, HIS 41, HIS 164, THR 26
5	Pralatrexate	-7.3	GLU 166, GLN 189, ARG 188, THR 26
6	Pteroyltriglutamic acid	-8.3	CYS 145, HIS 163, HIS 41, LEU 141, MET 165, THR 26, THR 25, THR 26, THR 190
7	10-Formyl Folic Acid	-7.8	ASP87, GLN 189, HIS 41, HIS 164, MET 49, THR 190

Pteroyltriglutamic acid formed hydrogen bonds with the amino acids CYS 145, HIS 163, HIS 41, LEU 141, MET 165, THR 26, THR 25, THR 26, THR 190 and showed promising inhibiting activity of Covid-19 main protease M^{pro}. The docking of folic acid with COVID-19 main protease showed significant interactions with the affinity of -8.2 kcal/mol. The major interactions between folic acid and the protease are characterized by hydrogen bond. Pralatrexate and Pemetrexed were the least effective ligands against Covid-19 main protease M^{pro}.

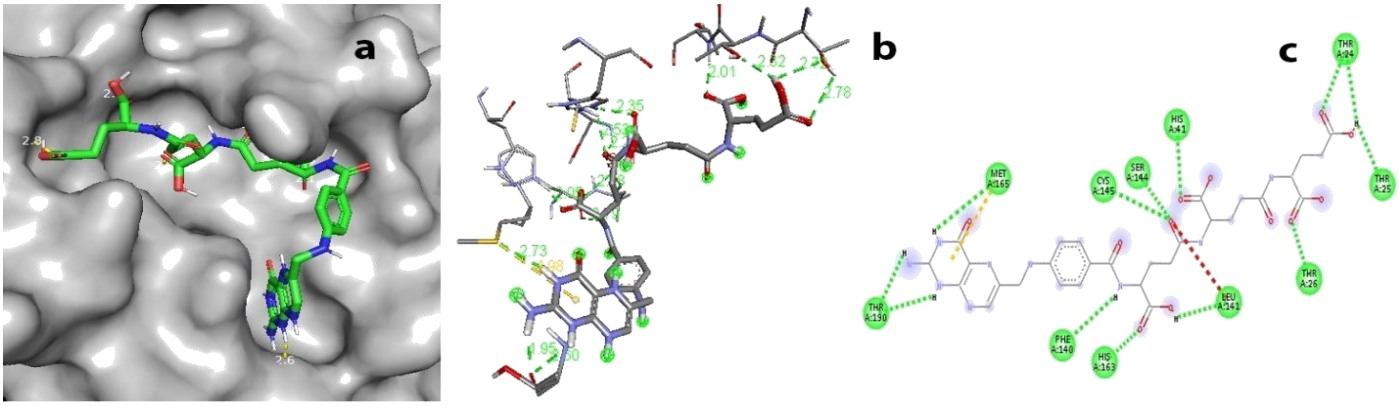

Fig. 2: Pteroyltriglutamic acid docked in Covid-19 main protease M^{pro} (PDB ID 6LU7) with (a) Best binding mode in the pocket of protein (with ligand as green color sticks), (b) Amino acid residues involved in interaction (with ligand as grey sticks) and (c) Binding interaction of Pteroyltriglutamic acid with amino acid with hydrogen bond (green dash line).

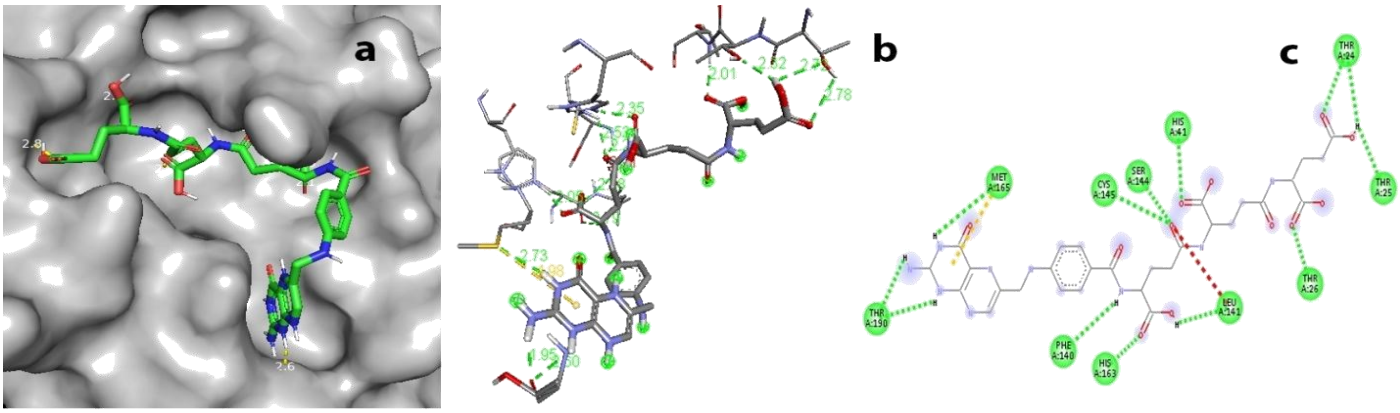

Fig. 3: Folic acid docked in Covid-19 main protease M^{pro} (PDB ID 6LU7) with (a) Best binding mode in the pocket of protein (with ligand as green color sticks), (b) Amino acid residues involved in interaction (with ligand as grey sticks) and (c) Binding interaction of Folic acid with amino acid with hydrogen bond (green dash line).

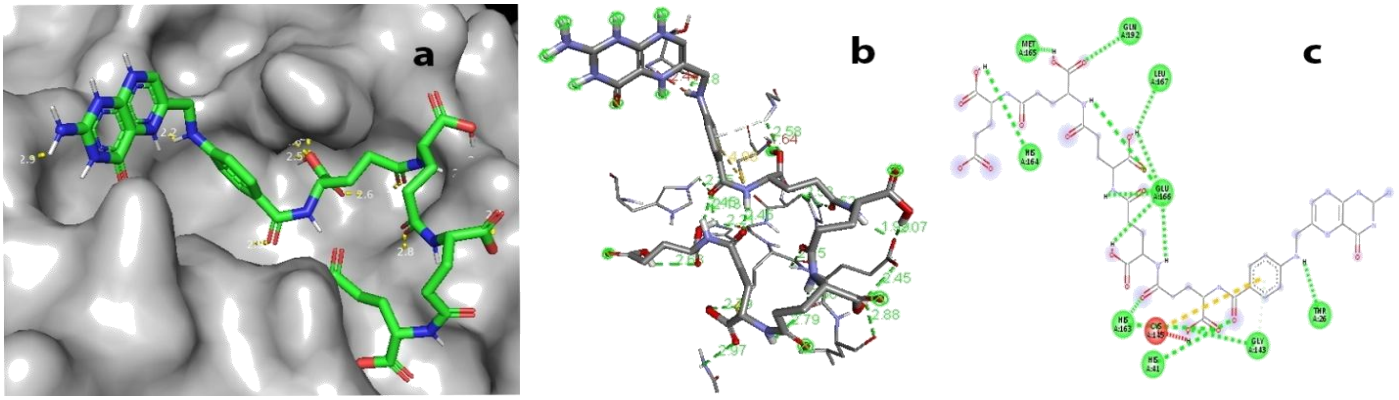

Fig. 4: Pentaglutamyl folate docked in Covid-19 main protease M^{pro} (PDB ID 6LU7) with (a) Best binding mode in the pocket of protein (with ligand as green color sticks), (b) Amino acid residues involved in interaction (with ligand as grey sticks) and (c) Binding interaction of Pentaglutamyl folate with amino acid with hydrogen bond (green dash line)

4. CONCLUSION

The metabolic pathway of the COVID-19 dependents on the protein main protease M^{pro}. Among the 7 ligands, Pteroyltriglutamic acid showed a better binding affinity for the target protein. The folate analogues compounds screened in this study is already in use in the medical field. Therefore, from the current molecular docking study it has been concluded that the folate analogues compunds can act as M^{pro} inhibitor and the can be used as a potential medicines to fight the Covid-19 pandemic.

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