Nat. Volatiles & Essent. Oils, 2023;10(1):44-49

NVEO
Natural Volatiles & Essential Oils

Molecular Docking Approach On Potential Of 2,6-Diphenylpiperidin-4-Ol Derivatives To Inhibit Covid 19 Mainprotease

M.Meenakumari[1*], R. Girija[2]

[*1]Department of Chemistry, Queen Mary's college, Chennai
[2]Bioinformatics Infrastructure Facility Center, Queen Mary's college, Chennai

***Corresponding Author:** M. Meenakumari
*Department of Chemistry, Queen Mary's college, Chennai, Email: meeena89@gmail.com, 9176622989.

Abstract:

COVID-19 is a disease caused due to SARS-CoV-2, the deadliest global spread of recent years. The virus spreads among humans through any type of contact between each other, through the air, and also through contaminated surfaces. The Main Protease (M^{Pro}) of SARS-CoV-2 is one of the expected targets in the development of new drug molecules for the disease. Some drugs like "chloroquine" and "remdesivir" have been used for therapeutics of COVID-19, even though the effect of these compounds is still mysterious. In the present study, the ligand and structure-based study was applied to compute the interaction with 2,6-diphenylpiperidin-4-ol derivatives on COVID-19 main protease. 2,6-diphenylpiperidin-4-ol derivatives (M1-M7) were found to show a similar structure of some Antiviral drugs via Qikprop. *In silico* docking study was carried out by 2,6-diphenylpiperidin-4-ol derivatives using Schrodinger Maestro 12.4 on SARS-CoV-2 M^{Pro} receptors with PDB ID of 5R84. The potential imperative energy were calculated and the interactivity of each ligand were analyzed. To further expound the binding sites of the inhibitors for 5R84 active sites of three docking programs such as, Glide Score, Extra Precision (XP) Energy, Glide Energy were used. The attribute of the actively binding sites were then set out by the conformations of docking results. In conclusion, the 2,6-diphenylpiperidin-4-ol derivative with the best binding energy was noted to have high potency against COVID-19 Mainprotease.

Keywords: SARS-CoV-2, 2,6-diphenylpiperidin-4-ol derivatives, *In silico,* Schrodinger Maestro 12.4, PDB ID: 5R84.

1.INTRODUCTION:

Covid 2019 commenced in Wuhan city in December 2019, rapidly spread throughout China and affected around 210 countries and territories in a matter of weeks. The pathogen was identified as a novel enveloped RNA beta coronavirus that has a ontogeny similarity to SARS-CoV and named as corona virus 2 (SARS-CoV-2)[1]. Patients infected with this suffer from severe acute respiratory syndrome as a result this may tend to death due to major alveolar damage and progressive respiratory failure[2]. According to World Health Organization (WHO) situation report on 3rdJuly 2021, the virus had gave rise to 19.4Cr infections and 41.6L deaths all over world. Therefore, a global response is fiercely needed to find effective drugs against this uncommon pandemic disease. Till date, there is no specific treatment approved to treat against COVID-19 disease however several protocols were tested such as chloroquine derivatives[3], azithromycin[4] and convalescent plasma[5]. Recently published high-resolution structure of "COVID-19 protease"[6,7]created the opportunity to develop its inhibitor and gave an essential key to control virus transcription and

replication[8,9].By comprehensive breakdown of protein into smaller peptide processing, the useful polypeptides are emancipated from the polyproteins, mainly by a 33.8kD a main protease (M ^{pro}) which is also known as 3C-like protease. The importance of M ^{pro} in corona virus life cycle, and the absence of similar congruent in humans, introduce M ^{pro} as an fascinating target for antiviral drug design[11]. Thus targeting Crystal Structure of SARS-CoV-2 main protease, 2,6-diphenylpiperidin-4-ol derivatives[16] (M1-M7) inhibitors leads directly to the down regulation of client proteins and attains Antiviral activity. 2,6-disubstituted-piperidine derivatives[17] are witnessed as an important building block of many alkaloid natural products, therapeutic drugs and they play key role as intermediates for synthesis of many organic compounds[18,19]. The substituted Piperidine derivatives are found to possess of various antimicrobial activities including anti-inflammatory, anti-tuberculosis, antipyretic, antibacterial, antifungal, etc [20,21]. The antimicrobial and antiviral activities are improved or declined when the conformation of piperidine is interchanged due to substitution on different position. Hence, analyzing the conformation of compound has become valuable in recent years[22]. Accordingly, Our investigation has demonstrated that substituted Piperidinols has a noteworthy role in designing an antiviral drug.

2.MATERIALS AND METHODS

2.1.Materials

The software used was the Schrodinger Maestro 12.4, Glide. Three-dimensional structures of receptor were obtained from Protein Data Bank website. The ligands ADMET property was studied with Molispiration software tool.

2.2.Ligands preparation

Structures of ligands were sketched and saved in SDF format and imported by selecting file. The imported ligands (M1-M7) were set to minimize under force field OPLS3e. Minimization calculations were performed on all structures of 2,6-diphenylpiperidin-4-ol derivatives.

2.3.Receptors preparation

The receptors used were SARS-CoV-2 M^{Pro} (PDB ID 5R84) each with a co-crystal ligand of 2-cyclohexyl- ~{N}-pyridin-3-yl-ethanamide respectively[13] The resolution is in the range of 1.83Å. Three-dimensional structures of receptor proteins was obtained from the website of Protein Data Bank.

2.4.ADMET Calculation

The study affirmed molecular properties, drug likeness, target prediction, exploring in search for a lead compound among all 7 derivatives of 2,6-diphenylpiperidin-4-ol. On the table1 below the distribution of Biological activity scores for the six most important drug classes.

S. No	milog P	TSPA	n Atoms	MW	nON	nOHNH	nViolations	nrotb	volume
M1	1.2	32.26	19	253.34	2	2	0	2	249.12
M2	3.00	32.26	21	281.40	2	2	0	2	281.94
M3	3.97	32.26	21	281.40	2	2	0	2	282.29
M4	4.97	32.26	23	309.45	2	2	0	4	315.89
M5	4.47	32.26	22	295.43	2	2	0	3	299.09
M6	3.67	32.26	23	309.45	2	2	0	4	315.55
M7	3.34	32.26	22	295.43	2	2	0	3	298.74

Table1. Result of ADMET Properties

S. No	GPCR Ligand	Ion channel modulater	Kinase Inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
M1	-0.08	-0.00	-0.36	-0.26	-0.16	-0.09
M2	0.07	-0.04	-0.34	-0.10	-0.01	-0.08
M3	-0.10	-0.15	-0.50	-0.26	-0.08	-0.22
M4	0.01	-0.08	-0.04	-0.11	0.05	-0.13
M5	-0.05	-0.13	-0.49	-0.17	0.01	-0.18
M6	0.13	-0.04	-0.38	-0.02	0.08	-0.06
M7	0.12	-0.04	-0.42	-0.01	0.07	-0.04

Table2. Result of Bioactivity Properties

2.5.Molecular Docking

Retrieved protein was prepared using the Protein Preparation Wizard in Maestro V 12.4 (Schrödinger, LLC, NY, USA, 2020). In this, bond orders were assigned, water molecules were removed, and OPLS3e force field was applied for minimization of the protein structure. The grid was generated using receptor grid generation panel in Maestro for receptor, by selecting active site amino acid residues (Tyr449, Asn487, Gly496, Thr500, Gly502, and Tyr505) of chain A of the spike RBD. The grid coordinates (i.e., X, Y, and Z) were respectively . The SARS-CoV-2 RBD has a twisted five stranded anti parallel β sheets (β1, β2, β3, β4, and β7) with short connecting loops & helices that form the core. SARS-CoV-2 RBD consist residues Arg319–Phe541. Analysis of the interaction surface of RBD-ACE2 reveals few contact points between RBD and ACE2. Tyr505 of RBD exhibits very stable hydrogen bonding suggesting an early contact point with ACE2. In addition, Tyr449, Gln493, Gln498, Thr500, Asn501, and Gly502 exhibit polar interactions with the ACE2 surface. Thus, all these amino acids of RBD comprise a suitable binding site to target the RBD of the spike protein with suitable drug-like molecules[14].

3.RESULT AND DISCUSSION:

3.1.Molecular Docking Analysis:

The molecular docking studies of designed ligands with protein active sites were performed by molecular docking program, Schrodinger Maestro 12.4 version to determine the various binding affinities of the compounds. The designed compounds are docked towards the SARS CoV-2 (5R84) inhibition activity. The compounds M6(Figure 6) showed good result to the receptor comparing with other compounds. The compounds M1, M2, M3, M4, M5, M6 and M7 have more Glide scores. This is due to vast lipophilic evidence and hydrogen bonding. The results are summarized in the Table 2. The best affinity modes of the top one docked compound (M6) with SARS CoV-2 having good Glide score are shown in Figure 2[15].

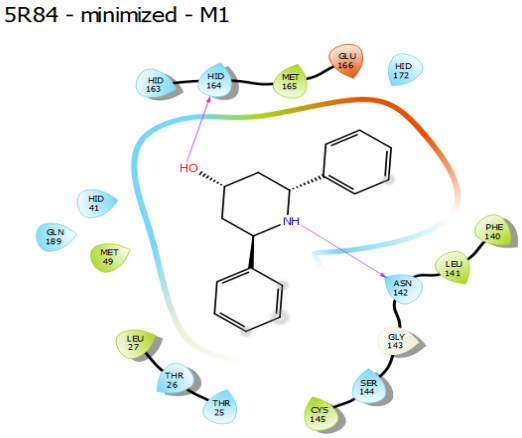


Fig 1. Protein ligand interaction profile M1

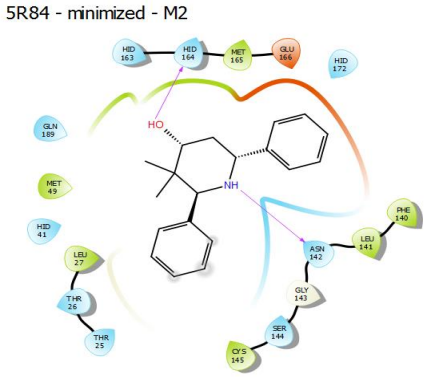


Fig 2. Protein ligand interaction profile of M2

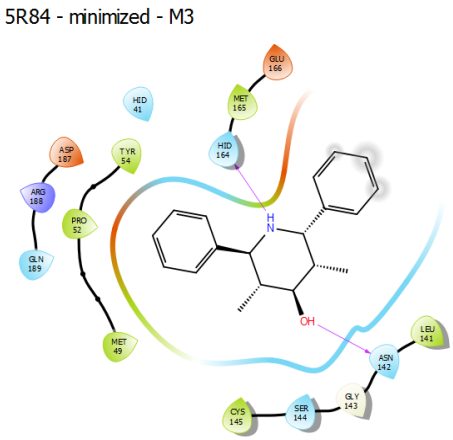


Fig 3. Protein ligand interaction profile of M3

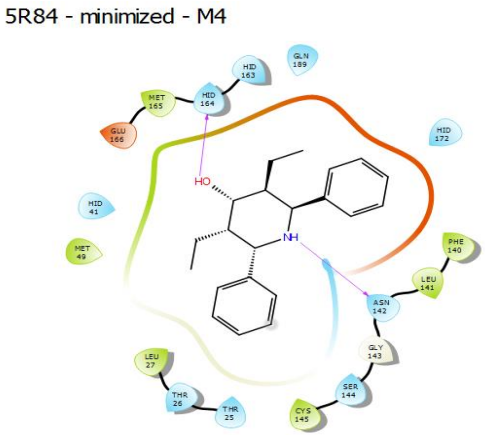
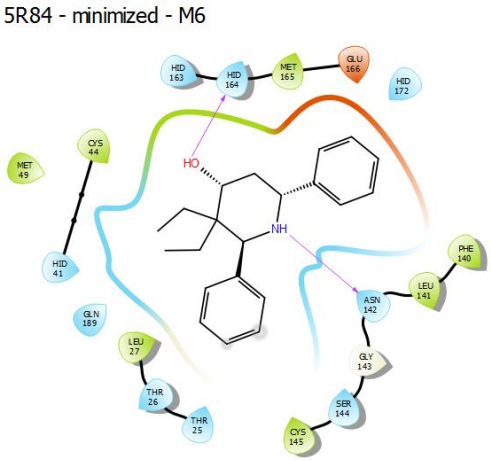


Fig 4. Protein ligand interaction profile of M4



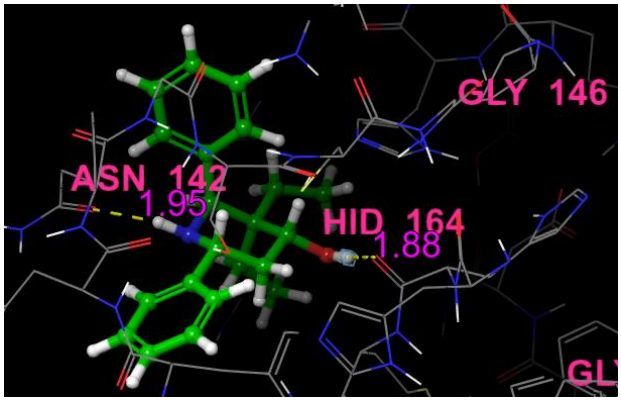


Fig 6. Protein ligand interaction profile of M6

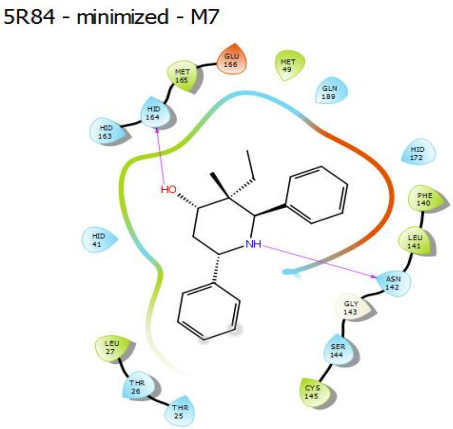


Fig 7. Protein ligand interaction profile of M7

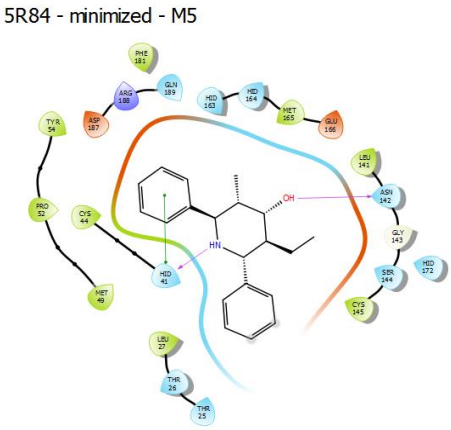


Fig 5. Protein ligand interaction profile of M5

TITLE	DOCKING SCORE	XP GSCORE	GLIDE GSCORE	GLIDE ENERGY	GLIDE EMODEL
M6	-6.789	-6.789	-6.789	-38.633	-50.488
M7	-6.135	-6.135	-6.135	-37.723	-48.089
M5	-6.07	-6.07	-6.07	-31.5	-37.799
M4	-5.963	-5.963	-5.963	-35.982	-51.676
M1	-5.943	-5.943	-5.943	-40.029	-47.351
M2	-5.911	-5.911	-5.911	-37.763	-47.36
M3	-4.499	-4.499	-4.499	-38.647	-49.661

Table 3. Results of Docking analysis of SARS CoV-2 Protein with2,6-Diphenylpiperidin-4-Ol Derivatives

4.CONCLUSION:

In conclusion, this study opens the opportunity for new compounds that have the potential to be developed in COVID-19 therapy as a SARS-CoV-2 M^{Pro}inhibitor. The enormous potential is mainly shown by seven ligands consisting of2,6-Diphenylpiperidin-4-Ol Derivatives which shows the lowest ΔG of receptors SARS-CoV-2 M^{Pro} used. All seven ligands have even better potential. The current *in silico* investigation is a preliminary work which necessitates future preclinical and clinical studies for verification of the results and expected to be the first step in development of 2,6-Diphenylpiperidin-4-Ol Derivatives in COVID-19 therapy.

5.ACKNOWLEDGEMENT:

* Bioinformatics Infrastructure Facility Center- Queen Mary's College (Autonomous) Chennai- 600005.

6.REFERENCE:

1. W. Guan, Z. Ni, Y. Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei and D. S. Hui, N. Engl. J. Med., 2020, 382, 1708–1720.
2. Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu and L. Zhu, Lancet Respir. Med., 2020, 8, 420– 422.
3. J. Gao, Z. Tian and X. Yang, BioSci. Trends, 2020, 14, 72–73.
4. P. Gautret, J.-C.Lagier, P. Parola, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V. E. Vieira and H. T. Dupont, Int. J. Antimicrob. Agents, 2020, 105949, DOI:
5. 10.1016/j.ijantimicag.2020.105949.
6. L. Chen, J. Xiong, L. Bao and Y. Shi, Lancet Infect. Dis., 2020, 20, 398–400.
7. Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, Y. Zhao, B. Zhang, X. Li, L. Zhang and C. Peng, bioRxiv, 2020, DOI: 10.1101/ 2020.02.26.964882.
8. L. Zhang, D. Lin, X. Sun, U. Curth, C. Drosten, L. Sauerhering, S. Becker, K. Rox and R. Hilgenfeld, Science, 2020, 368, 409–412.
9. O. M. Aly, ChemRxiv, 2020, DOI: 10.26434/ chemrxiv.12061302.v1.
10. K. Anand, G. J. Palm, J. R. Mesters, S. G. Siddell, J. Ziebuhr and R. Hilgenfeld, EMBO J., 2002, 21, 3213–3224.
11. A. Hegyi and J. Ziebuhr, J. Gen. Virol., 2002, 83, 595–599.
12. T. Pillaiyar, M. Manickam, V. Namasivayam, Y. Hayashi and S.-H. Jung, J. Med. Chem., 2016, 59, 6595–6628.
13. Yuan S, Chan S, Hu Z. Using PyMOL as a platform for computational drug design. Wiley Interdiscip Rev ComputMol Sci. 2017;7(2):1298. doi:10.1002/ wcms.1298.
14. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, et al. Structure of M^{pro} from COVID-19 virus and discovery of its inhibitors. Nature. 2020;582(7811):289-93. doi:10.1038/s41586-020-2223-**γ**.
15. Veeramachaneni, G. K., Thunuguntla, V. B. S. C., Bobbillapati, J., and Bondili, J. S. (2020). Structural and simulation analysis of hotspot residues interactions of SARS-CoV 2 with human ACE2 receptor.J. Biomol. Struct.Dyn. 38, 1–11. doi: 10.1080/07391102.2020.1773318.

16. Kalirajan R*, Pandiselvi M, Sankar S and GowrammaB Kalirajan R, Pandiselvi M, Sankar S and GowrammaB. SF Journal of Pharmaceutical and Analytical Chemistry 1(1) (2018).
17. Structure based molecular docking studies of 2,6-diphenylpiperidin-4-ol derivatives inhibition on Renin. R.Girija[1], M.Meenakumari[*] IJPBS.
18. A facile synthesis, antibacterial, and antitubercular studies of some piperidin-4-one and tetrahydropyridine derivatives Gopalakrishnan Aridoss a, Shanmugasundaram Amirthaganesan a, Nanjundan Ashok Kumar a, Jong Tae Kim a, Kwon Taek Lim a, Senthamaraikannan Kabilan b, Yeon Tae Jeong a,*
19. Takahata H, Ouchi H, Ichinose M and Nemoto, H Org. Lett. 2002, 4 (20), 3459.Honda T and Kimura M Org. Lett. 2000, 2 (24), 3925.
20. Balasubramanian S, Aridoss G, Parthiban P, Ramalingan C and Kabilan S Biol. Pharm. Bull. 2006, 29 (1), 125.
21. Jayabharathi J, Thangamani A, Padmavathy M and Krishnakumar B Med. Chem. Res. 2007, 15, 431.
22. Stereochemical effect on biological activities of new series of piperidin-4-one derivatives Periyasamy Venkatesana* and Thiyagarajan Maruthavananb.