How to Cite: Bhole, R.P., Karche, P.M., Shinde, Y., Kute, P.R., Gurav, S.S., & Wavhale, R.D. (2022) Design and Synthesis of Vitamin Drug Conjugate for its Probable Potential Against SARS-COV-2 Infections. *Bulletin of the University of Karaganda Chemistry, 108(4), 46-53.* https://doi.org/10.31489/2022Ch4/4-22-18

Article

Received: 31 August 2022 | Revised: 27 October 2022 | Accepted: 04 November 2022 | Published online: 02 December 2022

UDC 544.42+519.242.7 https://doi.org/10.31489/2022Ch4/4-22-18

R.P. Bhole[1*], P.M. Karche[1], Y. Shinde[1],
P.R. Kute[1], S.S. Gurav[2], R.D. Wavhale[1]

[1]Department of Pharmaceutical Chemistry, Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, India; [2]Goa College of Pharmacy, Panjim, Goa
*(*Corresponding author's e-mail: ritesh.bhole@dypvp.edu.in)*

Design and Synthesis of Vitamin Drug Conjugate for its Probable Potential Against SARS-COV-2 Infections

The novel corona virus infection had become a global epidemic due to its rapid spread. So, there is an urgent need to treat COVID-19 patients. The aim of this research was to hypothesize and examine vitamin drug conjugate as targeted moiety. The present scaffold may have potential role to fight against COVID-19 infection due to its antimicrobial, antioxidants and immunomodulatory activities. Here, we've highlighted the term Vitamin Drug Conjugate as possible therapy approach for SARS-COV-2 infection. As a result, we synthesize, characterized, and evaluated a Hydroxychloroquine — Folic Acid conjugate (HCQ-FA) by esterification mechanism to provide effective treatment against SARS-CoV-2 infection by enhancing therapeutic effect through synergistic mechanism, masking undesired side effects, and improving cellular internalization. By using prodrug, the efficacy and bioavailability of existing antiviral drugs could be improved. The structure of the conjugate was determined by spectroscopic data like IR, NMR, and mass spectra, which indicates that HCQ-FA conjugate formed by esteric conjugation. Molecular docking studies revealed that HCQ-FA conjugate shows good level of docking as well as binding interaction with main protease moiety. Molecular dynamic stimulation revealed that this conjugate shows good stability at the binding site of SARS main protease moiety and exhibits inhibitory activity against COVID-19 infection.

Keywords: Vitamin drug conjugate, SARS-COV-2, Hydroxychloroquine, Folic acid, Molecular modelling, Molecular Dynamic stimulation.

Introduction

Coronavirus infection (COVID-19) has received a lot of attention around the world due to its quick transmission within humans and extremely high mortality [1]. The coronavirus outbreak that began in Wuhan, China in December 2019 has become now a global disaster [2, 3]. The novel corona virus is also known as SARS-COV-2 and causes a contagious disease called COVID-19 [4, 5].

But there are currently no therapies for COVID-19 that have been approved by the FDA [6]. During the COVID-19 pandemic, significant efforts have been made to develop therapeutic methods for the treatment and prevention of SARS-CoV-2 infection, but still no drug therapy has proven effective against SARS-COV-2 infection. But there is hope on the drugs such as hydroxychloroquine, remdesivir, favipiravir, lopinavir and ritonavir, which are used in the treatment guidelines in many hospitals around the world, and these drugs play a vital role in prevention a novel coronavirus infection [2, 7–8]. However, it was found that each antiviral drug alone is ineffective in the therapy of COVID-19 individuals, particularly in severe instances. Combination drug therapy is used to increase their effectiveness, which invariably result in adverse effects. As a result, there is an urgent need for treatment alternatives necessary to manage the COVID-19 epidemic with minimizing adverse effects [1, 9]. Another way to prevent this disease is by enhancing immunity, as it plays a critical role in fighting against SARS-COV-2 infection [6–7]. Apart from this many studies have explored that vitamins play a critical role against SARS-COV-2 infection through antioxidant, immunomodulatory and antimicrobial effects. According to new research, significantly higher dosages of nutrients including vitamins D, B, C, E, Zinc, and Omega-3 fatty acids may have a positive impact, potentially reducing SARS-CoV-2 viral infection and duration of hospitalization. It has recently been found that deficiency of these vitamins is associated with COVID-19 progression and an increase in patient mortality [6–10]. So here we highlighted the emerging concept "Vitamin-Drug Conjugate" which could be potential therapeutic option to treat SARS-COV-2 infection. Although coronavirus illness is being continuously increasing, there is current-

ly no particular antiviral drug effective on COVID-19. So it is required to develop targeted drug delivery with minimal side effects. This requirement can be met by the development of a "Vitamin-Drug Conjugate" (targeted) [10–12].

To create a pharmacologically active novel chemical entity, a drug is coupled to the targeted moiety through a spacer during the synthesis of a vitamin-drug conjugate. Vitamin drug conjugates will be non-toxic, specifically internalize into infected cells and release the medications without loss of activity, reduce toxic effects by remaining stable in blood circulation, and provide a target-specific delivery without harming normal cells, will help to minimize side effects [13, 14]. A vitamin-drug conjugate is one of the most promising methods for treating illnesses including cancer, tuberculosis, and a range of viral infections while also enhancing the therapeutic result. It selectively delivers medicine to the intended target [15–18].

Hydroxychloroquine and folic acid were used as raw materials to synthesize vitamin drug conjugates in this work. In addition, high-yield synthetic procedures for conjugate synthesis are presented in this paper, as well as detailed characterization information. Molecular modeling studies were also performed to compare the binding affinity of the supplied synthetic conjugate to the significant protease of SARS-COV-2. Molecular docking study was conducted to comprehend how Hydroxychloroquine Folic Acid Conjugate (HCQFA) binds to the main protease of SAR-CoV-2. We ran the molecular dynamic (MD) simulation to better understand the complex's stability. According to docking experiments, the HCQ-FA compound effectively inhibits the primary protease of the SARS-COV-2 virus. The current prodrug strategy may also improve drug potency and bioavailability and offer efficient treatment for new coronaviruses [19].

Experimental

Materials: All of the reactants used in this experiment were of analytical grade. Hydroxychloroquine sulphate was purchased from BLD Pharmatech Pvt. Ltd. Folic acid was purchased from Loba Chemie Pvt. Ltd. N-Hydroxy Succinimide (NHS) and 1-(3-Dimethylaminopropyl)ethyl carbodiimide HCl (EDC·HCl) were purchased from Sisco research laboratories Pvt. Ltd. and 4-Dimethylaminopyridine (DMAP) was purchased from Research lab fine chem industries.

Instruments used: Melting point was determined by using melting-boiling point apparatus (Veego). TLC was performed by sing Silica Gel plates F254 on Aluminium sheets to monitor the reaction process and assess the purity of the product. Spectroscopic data were recorded using following instruments. The Shimadzu FT-IR 8400S FTIR spectrophotometer was used to record FTIR spectra. Tetramethysilane served as an internal standard, and DMSO was used as the solvent to acquire nuclear magnetic resonance spectra. Mass spectra were captured using a Shimadzu LC-MS 8040 mass spectrometer. Schrodinger software was used to conduct docking studies. A 100 ns molecular dynamic (MD) simulation was run using the AMBER18 programme.

Methodology:

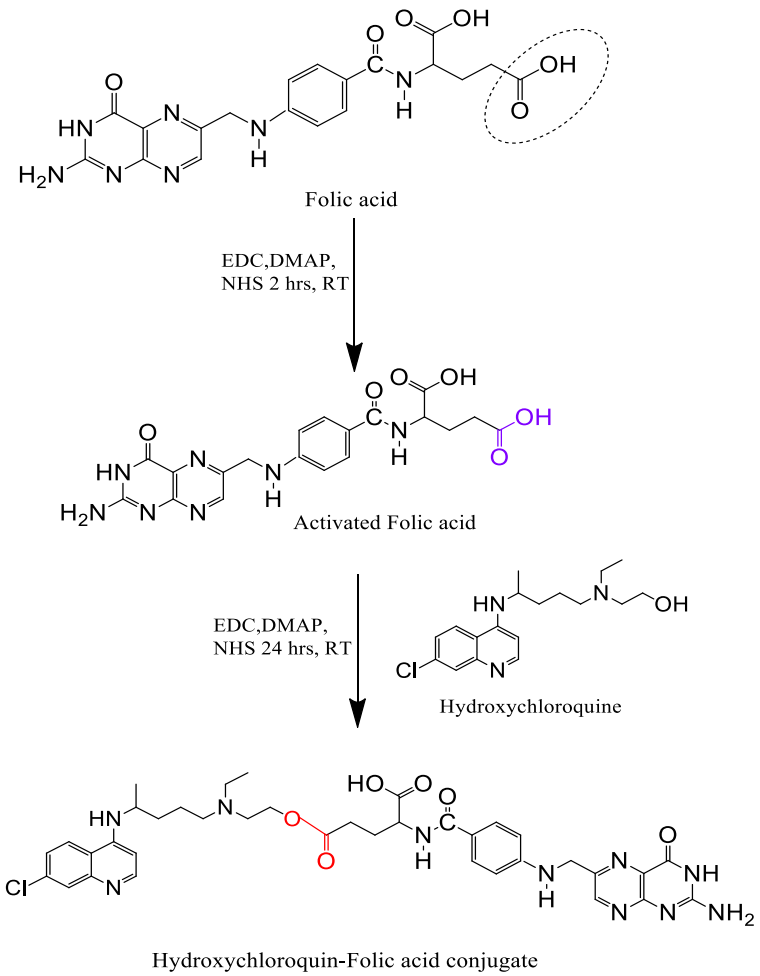
Hydroxychloroquine-Folic Acid Conjugate (HCQ-FA Conjugate)

HCQ-FA Conjugate were synthesized as per the synthetic route was shown in Scheme 1. An esterification method was used to synthesize HCQ-FA conjugate where HCQ hydroxyl group reacts with carboxyl group of folic acid result into formation of esteric derivative. Briefly, FA and EDC, DMAP, NHS were utilized to make activated folic acid and after that HCQ was added to generate HCQ-FA derivative.

The mixture containing Folic acid (440mg) were dissolved in 5 ml of distilled water and EDC, DMAP and NHS were added in the FA:EDC:DMAP:NHS in molar ratio of 1:2:3:1 to generate activated folic acid. The carboxyl group of FA were activated by stirred the reaction mixture using magnetic stirrer for 2 hrs. at room temperature by keeping the dark environment. After that, in the solution of activated folic acid, 400 mg of HCQ was added and left the reaction mixture to react for next 24 hrs. at room temperature by keeping dark environment. The reaction mixture was continuously monitored by TLC. The reaction was terminated once folic acid and HCQ were no longer present in the reaction mixture, and the product was then isolated using column chromatography. The given separated solution was then filtered and evaporated at 40°C in a rotary evaporator. The synthesized product's yield and Rf values were recorded.

Physical and Spectral data values of HCQ-FA Conjugate:

M.P. — 186–188 °C; IR (KBr, 4000–400 cm^{-1}) 1737.92 C=O (ester), 1693 (C=O carboxylic), 3093 (C-H stretch), 3338.89 (N-H stretch), 1417.73 (C-C stretch), 1291 (C-N), 2555 (O-H), 1635 (N-H); ^{1}H NMR (DMSO, 500 MHz): δ (ppm) = ^{1}H NMR δ = 6.5 to 8.5 (10H, Ar-H), 1.15 (t, 3H,), 1.17 (t, 3H), 1.37 (p, 2H), 1.44 (q, 2H), 2.35 (t, 2H), 2.43 (t, 2H,), 4.35 (t, 2H,), 4.39 (d, 2H), 4.55 (q, 1H), 11.5 (s, 1H), 6.63 (s, 2H), Ms: m/z(%) =759.04 (M+).



Scheme 1. Synthetic route of Hydroxychloroquine-Folic Acid conjugate

Molecular docking studies

The Schrodinger suite's Glide module was used to perform extra-precision (XP) molecular docking on the compounds. A grid generating approach was used to determine the binding location prior to the docking studies. The already-bound ligand was used as a reference site for the grid generation using the Glide grid module. The experiment involving docking also made use of the created grid. To lessen the potential of non-polar components on drug molecules, the van der Waals radii and scaling factor for the docking approach were set to 0.80 and 0.15, respectively. Throughout the entire docking protocol, the ligands were unrestricted. A maximum of five optimal postures for each ligand could be provided by post-docking minimization, which could then be included in the docking output file as reduced docked structures. The docking approach enables the drug molecules to be flexible. Each molecule's RMSD, docking score, glide score, and binding energy were noted.

Molecular Dynamics (MD) Simulations

In order to investigate the structural, energetic, and steric refinement of the docked complex, an all-atom MD simulation lasting 100 ns was carried out using the AMBER18 software. A total of 24,515 water molecules were present in the system when the docked complexes were submerged in truncated TIP3P water octahedrons. To neutralize the system and reach an ionic strength of 0.1M (which mimics the physiological pH), enough Na^+ and Cl^- counterions were added. Using the PMEMD, the complete MD simulation experiment was run on the Nvidia V100-SXM2-16GB Graphic Processing Unit. The Computational Shared Facility (CSF3) at the University of Manchester in the UK has a CUDA module installed. Simulations were carried out utilizing the Langevin thermostat at 300 K, a Monte Carlo barostat at 1 atm, and volume exchange attempts every 100 fs. The integration step used was 2 fs. Using the SHAKE algorithm, covalent bonds, including hydrogen, are restricted. An 8-cutoff was used for short-range nonbonded interactions, while the particle mesh Ewald approach was used to handle long-range electrostatics. For a total of 10 ns, equilibration involved cycles of NVT and NPT equilibration. A 100 ns production MD run was completed. CPPTRAJ was

used to assess the root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and other interactions along the entire trajectory, obtaining configuration measurements every 4 ps.

Results and Discussion

Scheme 1 shows the synthesis process for the HCQ-FA conjugate. Melting point and TLC tests were performed on the synthesized conjugate to ensure that it was pure and homogeneous. The structures of HCQ-FA Conjugate were ascertained through the use of IR, NMR, and mass spectrometry. Results from IR, NMR, and mass spectrometry were listed in the experiment section. In order to determine the conjugate's binding affinity to the SARS-COV-2 Main protease, molecular docking and MD stimulation studies were conducted. The results of MD stimulation of the HCQ-FA Conjugate and molecular docking investigations have also been presented in the experimental section.

FTIR

In the IR spectra of HCQ-FA, the primary peaks observed for C=O carboxylic acid 1693 cm^{-1}, 3093 cm^{-1} for C–H aromatic stretching, 3338.89 cm^{-1} for N-H stretching. The C-N and O-H stretching were observed at 1291 and 2555 cm^{-1}. Peaks at 17237.92 cm^{-1} for C=O of ester which indicate the formation of HCQ-FA conjugate through the formation of esteric bond. The development of an esteric linkage is only seen in the IR spectra of HCQ-FA conjugate but not observed in other molecules.

NMR

HCQ-FA Conjugate shows ^{1}H NMR at δ values, 4.35 (t, 2H,), 4.39 (d, 2H), 4.55 (q, 1H) respectively. The HCQ-FA Conjugates NMR spectra indicate peaks at the above-mentioned δ values, confirming the structure of the HCQ-FA Conjugate. Peaks in the 3-5 ppm range suggest the development of an esteric bonding in the conjugate.

Mass Spectroscopy:

The structural conformation of HCQ-FA conjugate was determined using mass spectra. The molecular ion peak at 759.04 m/z in the mass spectra of HCQ-FA conjugate confirms the conjugation of HCQ with Vitamin Folic acid through the development of an esteric linkage and confirms the synthesis of the final product, i.e., HCQ-FA conjugate.

Molecular modeling:

Molecular docking study was performed to comprehend how Hydroxychloroquine Folic Acid Conjugate (HCQFA) binds to the main protease of SAR-CoV2. The inhibitor N3 was complexed with the main protease of SAR-CoV-2 in the crystal structure (PDB:6LU7). Water molecules and other crystallographic solvents were removed from the targe receptor during processing, and the protein was reduced according to the Glide protein preparation methodology. The HCQFA was docked using the extra precision (XP) technique, and the Grid generation was carried out using N3 as the reference ligand. In comparison to hydroxychloroquine (–6.3 Kcal/mol), the best docked pose had a dock score of –7.4 Kcal/mol (Fig. 1). Thus, it was established that the target protein binds more strongly when the HCQ-FA conjugate is formed.

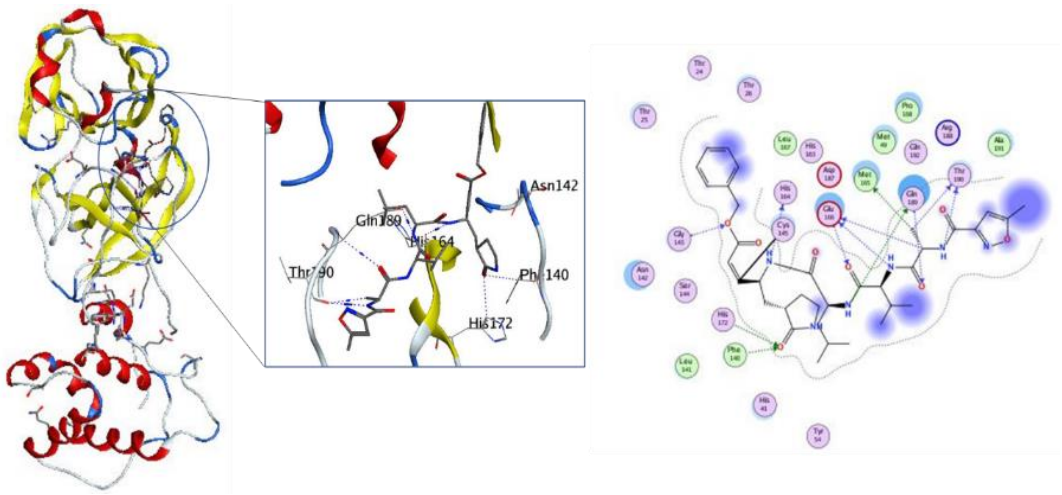


Figure 1. Docked complex of HCQFA with the SAR-CoV-2 main protease, the highlighted region shows the 3D image of protein ligand interactions and the 2D image sows the formation of various interaction between the ligand and receptor

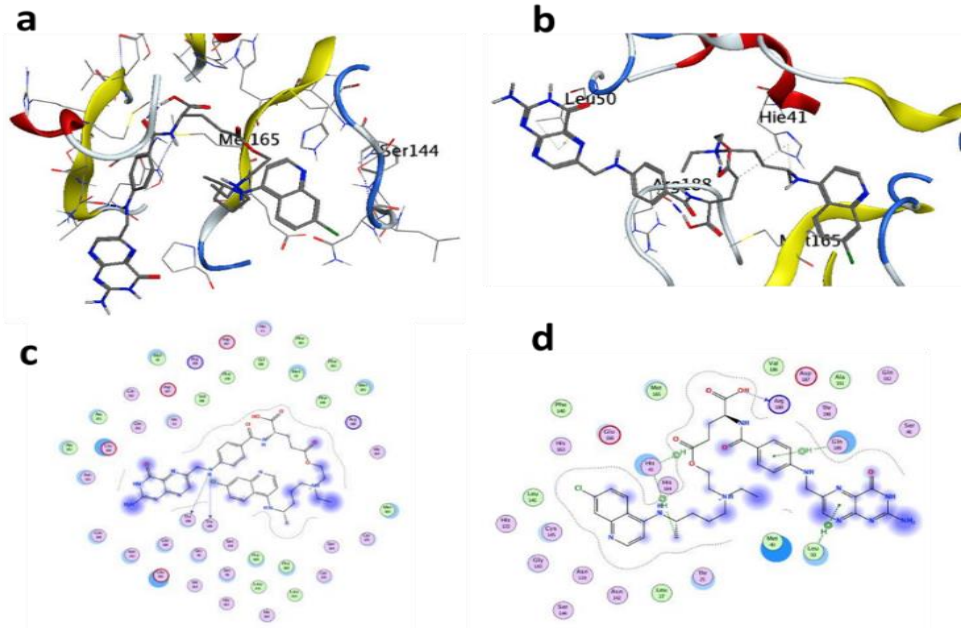
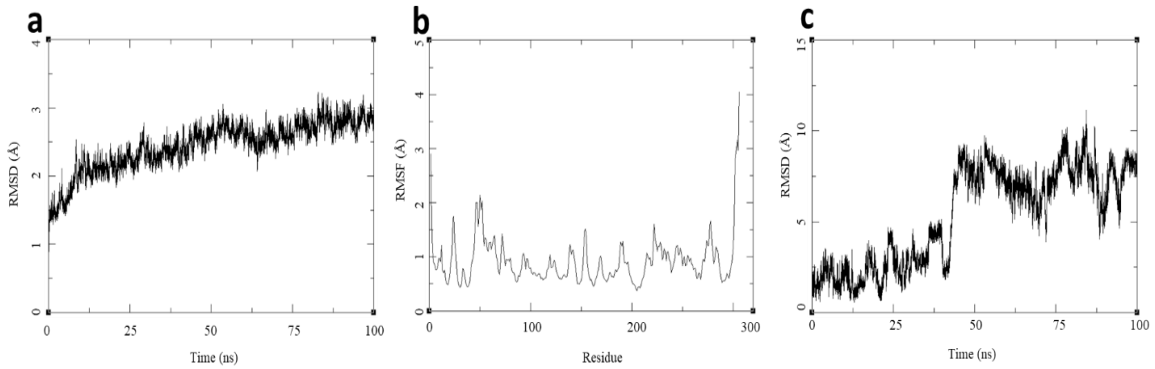


Figure 2. The figure 2*a*, *c* and 2*b*, *d* shows the initial and final conformations from the simulation of the protein-ligand complex for 100 ns

The ligand was seen to create multiple hydrogen bonds with the receptor's active site residues. The most significant ones are displayed in the three-dimensional (3D) schematic of the ligand-receptor interaction, where hydrogen bonds are formed by the amino acids Thr190, Gln189, His164, His172, Phe140, and Asn142.

We ran the MD simulation to better understand the stability of the complex. Figures 2a, 2b, and 2d show the simulation's initial and final conformations, respectively, while Figure 3 displays the findings from an examination of the complex's MD trajectory data.



a — Protein RMSD; *b* — Protein RMSF; *c* — Ligand RMSD

Figure 3. The trajectory analysis of the Protein-ligand complex

According to the MD simulation, the receptor residues engage in a number of novel interactions with HCQFA throughout the simulation, including the creation of hydrogen bonds with Met165 and Ser144 (Fig. 2*a*, *c*). The last frame of the MD simulation underwent examination, and it revealed the creation of hydrogen bonds with Arg188, His41, and His164. The conjugate's phenyl ring and the residue Gln180 interact through an arene (Fig. 2). With the use of CPPTRAJ and XMGRACE software, the MD trajectory was analyzed and graphs were created. The protein's RMSD points to a seamless transition and convergence between 1.5 and 3.0 Å. The conjugate's phenyl ring and the residue Gln180 interact through an arene. Throughout the simulation, the RMSF for the majority of the residues was below 2.0 Å additionally, it was discovered that the ligand experiences a conformational change that is reflected in its RMSD (Fig. 3*c*). At this time, the ligand's

RMSD varies between 1 and 5 and then rises sharply from 5 to 10 before stabilizing for the remainder of the simulation. All of these results point to good docking and even better stability over the majority of the MD simulation duration.

Conclusions

Hydroxychloroquine-Folic acid (HCQ-FA) conjugate was synthesized, characterized and evaluated. HCQ-FA conjugate may act as a novel approach against COVID-19 infection. HCQ-FA conjugate may exhibit synergistic antiviral activity against COVID-19 infection, indicating that this combination therapy could be used to combat the COVID-19 outbreak. This HCQ-FA conjugate was developed and investigated as a novel prodrug method to address HCQ's non-specificity and toxicology problems. The efficacy and bioavailability of the present antiviral drugs could be improved by using this prodrug method. Molecular docking studies demonstrated that HCQ-FA conjugate shows good docking score as well as greater binding towards target protein as compare to HCQ. MD stimulation revealed that this conjugate shows good stability at the binding site of SARS main protease moiety and exhibits inhibitory activity against COVID-19 infection. We concluded that this study could be useful for developing an effective therapeutic agent for SARS-COV-2 infection due to the additive effect of HCQ-FA conjugate. It can exhibit excellent antiviral activity and also helps to modulate immune system by synergistic mechanism.

References

1 Basiri, A., Pazhouhnia, Z., Beheshtizadeh, N. *et al.* (2021). Regenerative Medicine in COVID-19 Treatment: Real Opportunities and Range of Promises. *Stem Cell Rev and Rep, 17*, 163–175 https://doi.org/10.1007/s12015-020-09994-5

2 Khuroo, M.S. (2020). Chloroquine and hydroxychloroquine in coronavirus disease 2019 (COVID-19). Facts, fiction and the hype: a critical appraisal. *International Journal of Antimicrobial Agents*, *56*(3), 106101. https://doi.org/10.1016/j.ijantimicag.2020.106101

3 Bhole, R.P., Swamy, M.R., Wavhale, R., Bonde, C.G., & Chikhale, R. (2022). Design of potential vitamin-drug conjugate for enhanced anticancer activity. *Bulletin of university of Karaganda Chemistry*, 105(1), 6–14. https://doi.org/10.31489/2022Ch1/6-14.

4 Gates, B. (2020). Responding to COVID-19 — a once-in-a-century pandemic? *New England Journal of Medicine*, *382*(18), 1677–1679. https://doi.org/10.1056/NEJMp2003762.

5 Bhole, R.P., Bonde, C.G., Bonde, S.C., Chikhale, R.V., & Wavhale, R.D. (2021). Pharmacophore model and atom-based 3D quantitative structure activity relationship (QSAR) of human immunodeficiency virus-1 (HIV-1) capsid assembly inhibitors. *Journal of Biomolecular Structure and Dynamics*, *39*(2), 718–727. https://doi.org/10.1080/07391102.2020.1715258.

6 Carella, A.M., Benvenuto, A, Lagattolla, V., Marinelli, T., De Luca. P., Ciavarrella, G., Modola, G., Di Pumpo, M., Ponziano, E., & Benvenuto, M. (2020). Vitamin supplements in the Era of SARS-Cov2 pandemic. *GSC Biological and Pharmaceutical Sciences*, *11*(2), 007–019. https://doi.org/10.30574/gscbps.2020.11.2.0114.

7 Wang, C., Horby, P.W., Hayden, F.G., & Gao, G.F. (2020). A novel coronavirus outbreak of global health concern. *The Lancet*, *395*(10223), 470–473. https://doi.org/10.1016/S0140-6736(20)30185-9.

8 Bhole, R.P., Jadhav, S., Zambare, Y.B., Chikhale, R.V., & Bonde, C.G. (2020). Vitamin-anticancer drug conjugates: a new era for cancer therapy. *Journal of the Faculty of Pharmacy of Istanbul University*, *50*(3), 312.

9 Shakoor, H., Feehan, J., Al Dhaheri, A. S., Ali, H. I., Platat, C., Ismail, L. C., Apostolopoulos, V., & Stojanovska, L. (2021). Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? *Maturitas*, *143*, 1–9. https://doi.org/10.1016/j.maturitas.2020.08.003.

10 Alam, P., Alajmi, M., Siddiqui, N. A., & Basudan, O. (2014). Determination of bioactive marker glycyrrhizin in Glycyrrhiza glabra root and commercial formulation by validated HPTLC-densitometric method. *Journal of Coastal Life Medicine*. https://doi.org/10.3389/fphar.2021.659577.

11 Lai, C.C., Shih, T.P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International journal of antimicrobial agents*, *55*(3), 105924. https://doi.org/10.1016/j.ijantimicag.2020.105924.

12 Bhole, R., Bonde, C., Kadam, P., & Wavwale, R. (2021). A comprehensive review on photodynamic therapy (PDT) and photothermal therapy (PTT) for cancer treatment. *Turk Onkoloji Dergisi*, *36*(1), 125–132. https://doi.org/10.5505/tjo.2020.2400.

13 Wang, Y., Fan, G., Salam, A., Horby, P., Hayden, F. G., Chen, C., Pan, J., Zheng, J., Lu, B., Guo, L., Wang, C., & Cao, B. (2020). Comparative Effectiveness of Combined Favipiravir and Oseltamivir Therapy Versus Oseltamivir Monotherapy in Critically Ill Patients with Influenza Virus Infection. *Journal of Infectious Diseases*, *221*(10), 1688–1698 https://doi.org/10.1093/infdis/jiz656.

14 Bhole, R.P., & Bhusari, K.P. (2011). Synthesis and antitumor activity of (4-hydroxyphenyl)[5-substituted alkyl/aryl)-2-thioxo-1,3,-thiadiazol-3-yl] methanone and [(3,4-disubstituted)-1,3-thiazol-2ylidene]-4-hydroxybenzohydrazide. *Medicinal Chemistry Research*, *20*(6), 695–704. https://doi.org/10.1007/s00044-010-9371-9

15 Gombart, A.F., Pierre, A., & Maggini, S. (2020). A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. *Nutrients*, *12*(1), 236. https://doi.org/10.3390/nu12010236.

16 Calder, P.C. (2020). Nutrition, immunity and COVID-19. *BMJ Nutrition, Prevention & Health*, *3*(1), 74–92. https://doi.org/10.1136/bmjnph-2020-000085.

17 Andersen, K.G., Rambaut, A., Lipkin, W.I., Holmes, E.C., & Garry, R.F. (2020). The proximal origin of SARS-CoV-2. *Nature Medicine*, *26*(4), 450–452. https://doi.org/10.1038/s41591-020-0820-9.

18 Bao, L., Deng, W., Huang, B., Gao, H., Liu, J., Ren, L., Wei, Q., Yu, P., Xu, Y., Qi, F., Qu, Y., Li, F., Lv, Q., Wang, W., Xue, J., Gong, S., Liu, M., Wang, G., Wang, S., & Qin, C. (2020). The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *Nature*, *583*(7818), 830–833. https://doi.org/10.1038/s41586-020-2312-y.

19 Bourgonje, A.R., Abdulle, A. E., Timens, W., Hillebrands, J. L., Navis, G. J., Gordijn, S. J., Bolling, M. C., Dijkstra, G., Voors, A. A., Osterhaus, A. D. M. E., van der Voort, P. H. J., Mulder, D. J., & van Goor, H. (2020). Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). *Journal of Pathology*, *251*(3), 228–248. https://doi.org/10.1002/path.5471.

Р.П. Бхоле, П.М. Карче, Ю. Шинде, П.Р. Куте, С.С. Гурав, Р.Д. Вавхейл

SARS-COV-2 инфекцияларына қарсы ықтимал әлеуеті бар витамин-дәрілік конъюгаттың дамуы және синтезі

Жаңа коронавирустық инфекция тез таралуына байланысты жаһандық эпидемия мәртебесін алды. Осыған байланысты бүгінде COVID-19-мен ауыратын науқастарды тиімді емдеудің өзекті қажеттілігі туындап отыр. Зерттеудің мақсаты — мақсатты дәрі ретінде витаминді-дәрілік конъюгаттарды болжау және зерттеу. Мұндай конъюгаттың микробқақарсы, антиоксиданттық және иммуномодуляциялық белсенділігіне байланысты COVID-19 инфекциясымен күресуде айтарлықтай әлеуеті болуы мүмкін. Жұмыста SARS-CoV-2 инфекциясын емдеуге ықтимал тәсіл ретінде «дәрумен-дәрілік конъюгат» термині көрсетілген. Гидроксихлорохин-фолий қышқылы (ГХХ-ФҚ) конъюгаты этерификация механизмі арқылы синтезделді, синергетикалық механизм арқылы терапевтік әсерді күшейту, қажетсіз жанама әсерлерді жасыру және жасушалық интернализацияны жақсарту арқылы SARS-CoV-2 инфекциясын тиімді емдеуді қамтамасыз ету үшін сипатталды және бағаланды. Қолданыстағы вирусқақарсы препараттардың тиімділігі мен биотиімділігін осындай алдын ала препаратпен жақсартуға болады. Конъюгат құрылымы ИҚ, ЯМР және массалық спектрлер сияқты спектроскопиялық деректермен анықталды. Алынған спектрлік деректер ГХХ-ФҚ конъюгаты қосылыстың күрделі эфир реакциясы нәтижесінде пайда болғанын растайды. Молекулярлық докинг арқылы ГХХ-ФҚ конъюгаты жақсы тоғысу деңгейін, сондай-ақ протеазаның негізгі бөлігімен байланыстыратын өзара әрекеттесуін көрсетті. Молекулалық динамикалық модельдеуді қолдана отырып, SARS протеазасының негізгі бөлігінің байланысу орнында ГХХ-ФҚ конъюгатының жақсы тұрақтылығы және COVID-19 инфекциясына қарсы тежегіш белсенділігі атап өтілген.

Кілт сөздер: витамин-дәрілік конъюгат, SARS-CoV-2, гидроксихлорокин, фолий қышқылы, молекулалық модельдеу, молекулалық динамикалық модельдеу.

Р.П. Бхоле, П.М. Карче, Ю. Шинде, П.Р. Куте, С.С. Гурав, Р.Д. Вавхейл

Разработка и синтез витаминно-лекарственного конъюгата с вероятным потенциалом против инфекций SARS-COV-2

Из-за быстрого распространения новая коронавирусная инфекция получила статус глобальной эпидемии. В связи с этим сегодня существует острая необходимость в поиске эффективного лечения пациентов с COVID-19. Цель настоящего исследования состояла в том, чтобы выдвинуть гипотезу и изучить конъюгаты витаминов и лекарственных средств в качестве целевого препарата. Такой коньюгат может иметь значительный потенциал в борьбе с инфекцией COVID-19 благодаря своей антимикробной, антиоксидантной и иммуномодулирующей активности. В работе показан термин «витаминно-лекарственный конъюгат» как возможный подход к терапии инфекции SARS-CoV-2. Конъюгат гидроксихлорохин-фолиевая кислота (ГХХ-ФК) был синтезирован по механизму этерификации, охарактеризован и оценен с целью обеспечения эффективного лечения инфекции SARS-CoV-2 через усиление терапевтического эффекта за счет синергетического механизма, маскирования нежелательных побочных эффектов и улучшения клеточной интернализации. Эффективность и биодоступность существующих противовирусных препаратов могут быть улучшены с помощью такого пролекарства. Структуру конъюгата определяли по спектроскопическим данным, таким как ИК, ЯМР и масс-спектры. Полученные спектральные данные указывают на то, что ГХХ-ФК конъюгат образовался в результате сложноэфирной реакции соединения. Методом молекулярного докинга показано, что ГХХ-ФК конъюгат демонстрирует хороший уровень стыковки, а также связывающее взаимодействие с основной частью протеазы. С помощью молекулярно-динамического моделирования отмечена хорошая

стабильность ГХХ-ФК конъюгата в месте связывания основной части протеазы SARS и ингибирующая активность в отношении инфекции COVID-19.

Ключевые слова: витаминно-лекарственный конъюгат, SARS-COV-2, гидроксихлорохин, фолиевая кислота, молекулярное моделирование, молекулярно-динамическое моделирование.

Information about authors*

Bhole, Ritesh Prakash (*corresponding author*) — PhD, Associate Professor, Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Sant Tukaram Nagar, Pimpri, Pune-411018, India: e-mail: ritesh.bhole@dypvp.edu.in; https://orcid.org/0000-0003-4088-7470

Shinde, Yogita — M. Pharm, Research Scholar, Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Sant Tukaram Nagar, Pimpri, Pune-411018, India; e-mail: shindeyogita48@gmail.com;

Karche, Payal Manik — M. Pharm, Research Scholar, Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Sant Tukaram Nagar, Pimpri, Pune-411018, India; e-mail: karchepayal@gmail.com; https://orcid.org/0000-0003-3725-1121

Kute, Payal Ramesh — M. Pharm, Research Scholar, Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Sant Tukaram Nagar, Pimpri, Pune-411018, India; e-mail: kutepayal99@gmail.com; https://orcid.org/0000-0003-4779-6408

Gurav, Shaliendra Shivaji — Professor, Goa College of Pharmacy, Goa; e-mail: shailugurav@gmail.com, https://orcid.org/0000-0001-5564-2121

Wavhale, Ravindra — PhD, Assistant Professor, Dr. D.Y. Patil Institute of Pharmaceutical Sciences and Research, Sant Tukaram Nagar, Pimpri, Pune-411018, India; e-mail: ravindra.wavhale@dypvp.edu.in, https://orcid.org/0000-0003-1614-9742

*The author's name is presented in the order: *Last Name, First and Middle Names*