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Design and synthesis of novel triazole based small molecules mimicking HDACi as new modular drugs candidate against Omicron and future variants of Sars-Cov-2

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Due to the multi-modal nature of coivd 19 infection, dual target inhibition simultaneously by a solo molecule can be helpful and a possible operative method against coivd 19 and its variants. Histone-deacetylase (HDAC) has been extensively examined as a useful type of anti-cancer molecule due to its dynamic part in numerous biotic biological progressions, for example cell-proliferation, cell-metastasis, and cell-apoptosis. Numerous HDACi (HDAC-inhibitors) like vorinostat, panobinostat are clinically permitted and their direct usage in covid 19 patients may be helpful. Therefore, in this work, we report five novel small molecules mimicking HDACi with a double targeting capability of HDAC and covid 19 causing proteins M^{pro} and its variant omicron S-protein. The strategy that has been employed is the use of simple click reaction to develop these compounds along with their *in silico* study as inhibitors of covid 19 infection.

Keywords: Small molecule library, Click chemistry, HDACi, Docking, Quantitative structure property relationship (QSPR), Drug likeliness

The Covid 19 and its variants use its spike glycoproteins, which boost the entry to the cells by binding with human angiotensin-converting enzyme 2 (ACE2) receptor[1]; thus it is a prospective drug target. If a drug or small molecule can free the Spike-receptor-binding domain-ACE2 in a superior way from the infecting virus, then it can be appreciated as a decent approach to governing the range of infection. Along with these arguments, a cysteine protease 3-chymotrypsin-like protease (3CLpro) or the main protease (Mpro) was established as a necessary factor for the life cycle of the Sars-Cov-2[2,3] and its variants[4], like the new omicron variant of the Sars-Cov-2 virus - B.1.1.529. In this study, we design five triazole-based novel small molecules mimicking HDACi against the Sars-Cov-2 virus and its omicron variants.

HDAC plays a significant part in tumor-cell growth and expansion[5] and is an essential target amongst epigenetic regulators and its enzyme catalyzes the de-acetylation process of histones and non-histones[6]. The three main HDACi pharmacophores[7] are a cap group for surface recognition, a zinc-binding-group (ZBG), and a chain linker of 5 to 6 carbon approximately required to connect the cap-group and the ZBG[8] (Fig. 1). HDACi's have revealed potential in treatment of psychiatric problems, like schizophrenia so that it might be good against viral infection as well. Hence, we synthesized triazole molecules as modified HDACi (Fig. 2), studied binding potential against main protease (Mpro) protein of Sars-Cov-2 theoretically with the help of docking.

Materials and Methods

Reagents

All of the reagents were of analytical grade and were acquired from Sigma-Aldrich Chemicals Pvt. Ltd. All of the solvents used were of spectral grade and further dried by standard procedures. Analytical thin-layer chromatography (TLC) was accomplished on precoated (0.25 mm) silica gel plates (Merck, TLC Silica Gel 60 F254, Cat. No. 1.05554.0001). ^{1}H and ^{13}C NMR spectra were documented on AVANCE 400 MHz FT-NMR spectrometer, Bruker Biospin AG using dimethyl sulfoxide-d6 (99.8%D, Cambridge Isotope Laboratories, Inc., Cat. No. DLM-10-S-25).

# Both the authors have contributed equally to the work.

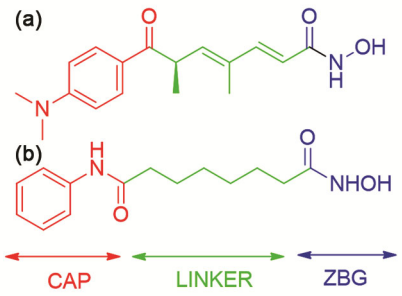


Fig. 1 — HDAC inhibitors (A) Trichostatin A (Natural HDACi); (B) SAHA (Vorinostat) and their dynamic functionality. (ZBG – Zinc Binding Group)

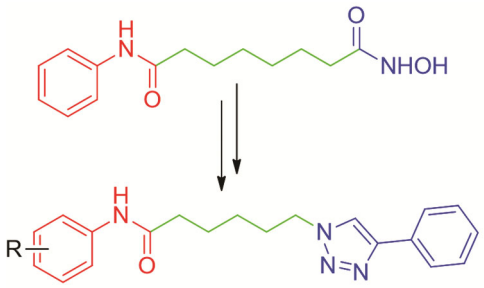
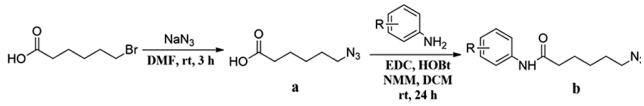


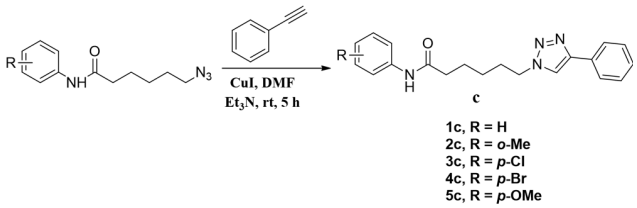
Fig. 2 — Schematic illustration of our modified HDACi and its relation with SAHA (Vorinostat)



Scheme 1 — Synthesis of different azide for click reaction

General synthetic procedure of N-phenyl-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide and its derivatives

6-Azidohexanoic Acid was synthesized rendering to the literature[9] technique by stirring 6-Bromohexanoic Acid with sodium azide in DMF for 3 hrs and the ^{1}H NMR data coincides fine with the previously reported literatures. In a 50 mL R.B. (round bottom) flask, 6-azidohexanoic acid (250 mg, 1.63 mmol) dissolved in 2.5 mL of DCM, NMM (0.24 mL, 1.96 mmol), HOBt (0.242 g, 1.63 mmol), and EDC (0.312 g, 1.63 mmol) were added and stirred for 15 min at r.t. Aniline and its derivatives (3.26 mmol) added in portion and stirred again for 24 h, as shown in Scheme 1. The reaction advancement was checked by TLC, the reaction mixture was distributed into water, and extraction was done using ethyl acetate (EtOAc) as solvent. The layer was washed with saturated $NaHCO_3$ solution followed by saturated NaCl (Brine) solution. The solvent layer was dried with anhydrous sodium sulphate (Na_2SO_4), and



Scheme 2 — Synthesis of triazoles by using click reaction

the solvent was vaporized to yield solid products. The product was then filtered over column chromatography using 10% EtOAc in petroleum ether[10-13]. The isolated yield approximately 69%. The Copper catalyzed click reaction to make 1,3 triazoles was done by adding phenylacetylene to azide[14,15] molecules in the presence of copper iodide (CuI) in dimethylformamide (DMF) for 5 hours, Scheme 2.

Molecular Docking

The crystal structure of protein M^{pro} and omicron S-protein was taken in PDB format from RCSB Protein DataBank (PDB) (http://www.rcsb.org/pdb), 6LU7 and 7WOP (PDB ID)[16]. We have performed the docking procedure according to our published papers[17-21]. As per the docking practice, the exclusion of all water and solvent particles, any residues in co-crystallized form, and any mirror chain were prepared using UCSF-Chimera software[17]. The following part is the protein-structure preparation, which is also completed in Chimera. The protein structures were made by conveying the hydrogen atoms, charge and energy minimization using the Dock-Prep tool. The charges were consigned according to the AM1-BCC method, which swiftly and proficiently generates high-quality atomic charges for the protein-structure, and the charges were computed by the ANTECHAMBER algorithm[22]. Energy minimization was completed using 600 steepest descent-steps with 0.020 Å step-size with an update interval of 9. The protein energy minimization of 6LU7 and 7WOP were auxiliary done with Swiss-PDB (SPDBV) viewer as it was confined with a co-crystallized ligand. The marked protein after minimization of energy was then kept in PDB format for docking usage[17,19].

Ligand preparation was performed according to our previously published papers[17,23,24]. The five novel triazole moieties molecules were designed by varying the architecture of the SAHA molecule (HDACi) in the two-dimensional (2D) arrangement, first using ChemDraw 12 ultra software, and then copying and pasting them in Chem-3D pro software to convert

them to 3D-SDF layout after minimizing the energy of the triazoles with MM2 operation. The rest of the method of preparation of the molecules as ligands for docking is the same as above. For picturing diverse arrangements, we used the software UCSF Chimera, Discovery Studio[25].

QSPR Analysis

Several linear-regression models developed by Potts and Guy[26], target at calculating the skin permeability coefficient (Kp), as Kp is linearly correlated with the size of the entities and their lipophilic nature ($R^2 = 0.67$). The more negative the value log K_p, the less skin permeant the molecule will be. The unit of K_p is cm s^{-1}. It is found with the help of the Swissadme web server.

Druglikeness

Another property of the swissadme web server is the prediction of druglikeness. Druglikeness was established from structure-dependent physicochemical examinations for the improvement of moieties as an oral drug or lead[27,28]. This concept is characteristically employed to accomplish the sieving of small molecules[29,30] and omit molecules[31,32] with physical properties dissenting with satisfactory pharmacokinetics[33]. These filters are regularly used for analyses by foremost pharmaceutical companies directed to develop the feature of their exclusive chemical pools. The Lipinski filter from Pfizer is the developer rule-of-5[34]. The other methods for measuring the druglikeness are Ghose[35] from Amgen, Veber[36] from GSK, Egan[37] from Pharmacia, and Muegge[38] from Bayer Pharmaceuticals.

Results and Discussion

Chemistry

N-phenyl-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide and other derivatives of novel triazole molecule was designed and synthesized using Click reaction. Initially, 6-azido-*N*-phenylhexanamide derivatives was prepared from commercially available 6-Bromohexanoic and different anilines (Scheme 1). From Scheme 1 the product isolated and forwarded for Click reaction shows yield of approximately ranging from 60-69%.

N-phenyl-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamides was finally synthesized by Click reaction between different 6-azido-*N*-phenylhexanamide derivatives and phenylacetylene (Scheme 2) with CuI at room temperature in presence of DMF and Et_3N.

The structure of triazoles synthesized by Click reaction (Scheme 2) shows yield of approximately ranging from 64-73% shown in Fig. 3.

Docking Results

The *in silico* interactions between the targeted protein 6LU7 and the novel triazole moieties were investigated using the molecular docking technique[39]. The calculations reveal the highest free energy change for these interactions as $\Delta G = -7.4$ kcal/mol and -7.3 kcal/mol for 6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-N-(o-tolyl)hexanamide for protein 6LU7-Mpro and 7WOP inside a grid box of −11 Å × 12 Å × 69 Å and 190 Å × 190 Å × 205 Å with size 33 Å × 33 Å × 33 Å along the x-, y-, and z-axes respectively (Table 1). The binding structures of the most stable conformer are shown in Fig. 4. The 2D structures showing the binding region and specific bonding to amino acid residues at the binding region for protein 6LU7-Mpro and 7WOP are given in Fig. 5 and Fig. 6 respectively. The 2D structures for protein 6LU7 reveal that SER A-144 residue is an important residue for inhibition, for protein 7WOP reveal that ASN C-32 residue is an

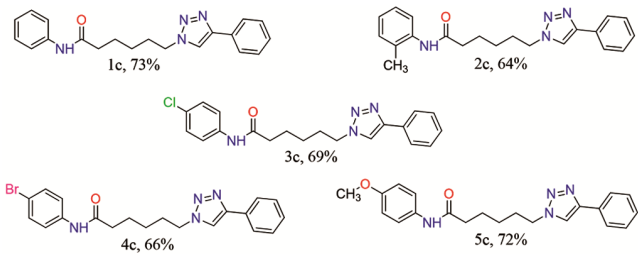


Fig. 3 — Structures of the synthesized triazole moieties

Table 1 — Docking scores of the trizole compound **1c** to **5c** with 6LU7 and 7WOP

Compd		Docking Score (Kcal/mol)	
		6LU7	7WOP
Control: N3 Ligand co-crystalized with 6LU7		–6.9	–
1.	**1c** - N-phenyl-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide	–7.1	–5.9
2.	**2c** - 6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-N-(o-tolyl)hexanamide	–7.4	–7.3
3.	**3c** - N-(4-chlorophenyl)-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide	–7.0	–6.4
4.	**4c** - N-(4-bromophenyl)-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide	–7.1	–6.1
5.	**5c** - N-(4-methoxyphenyl)-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide	–7.0	–5.6

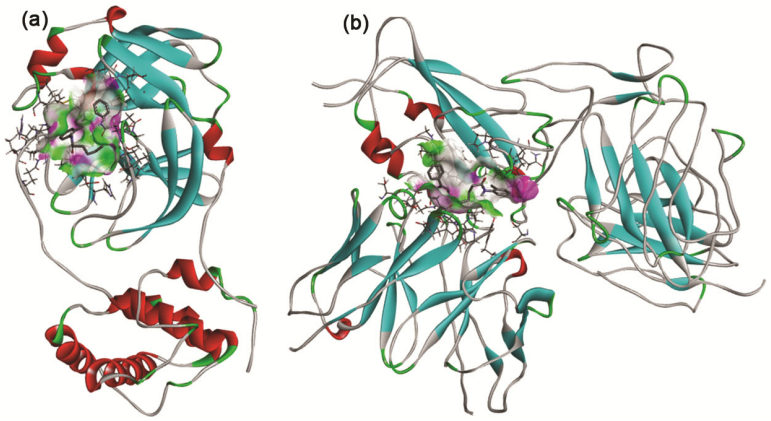


Fig. 4 — Ribbon structure of (a) protein 6LU7 with **2c** moiety; (b) protein 7WOP with **2c** moiety

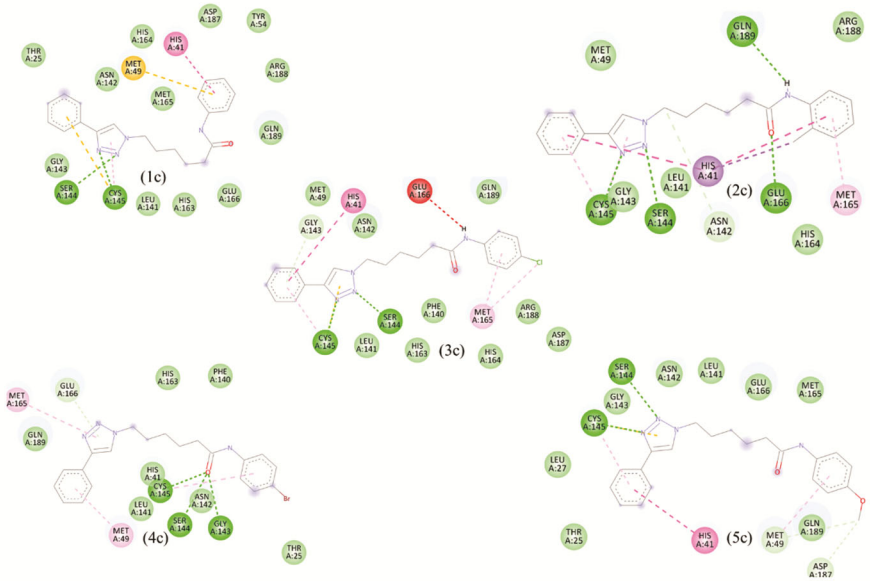


Fig. 5 — 2D Diagram of novel five triazoles in the binding pocket of 6LU7

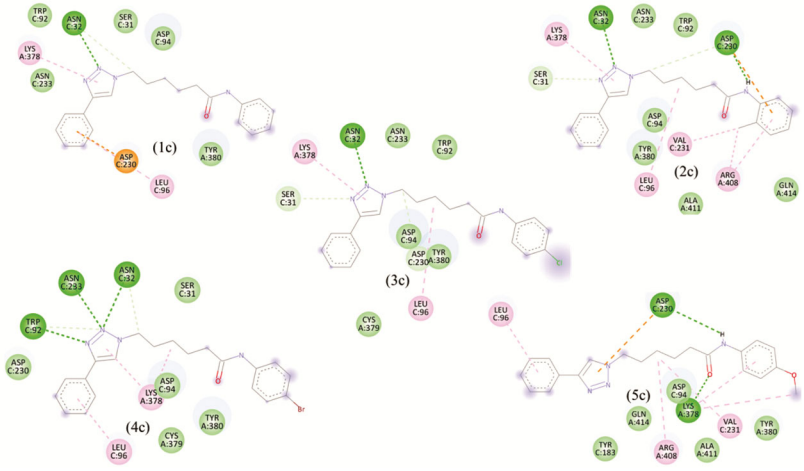


Fig. 6 — 2D Diagram of novel five triazoles in the binding pocket of 7WOP

Table 2 — QSPR data of triazole compound **1c** to **5c**

	Compd	Log Kp (According To QSPR)
1.	**1c** - N-phenyl-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide	–6.10 cm/s
2.	**2c** - 6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-N-(*o*-tolyl)hexanamide	–5.92 cm/s
3.	**3c** - N-(4-chlorophenyl)-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide	–5.86 cm/s
4.	**4c** - N-(4-bromophenyl)-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide	–6.09 cm/s
5.	**5c** - N-(4-methoxyphenyl)-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexanamide	–6.30 cm/s

Table 3 — Druglikeness results of triazole compound **1c** to **5c**

	Druglikeness				
Rules	**1c**	**2c**	**3c**	**4c**	**5c**
Lipinski's	Checked	Checked	Checked	Checked	Checked
Veber's	Checked	Checked	Checked	Checked	Checked
Ghose's	Checked	Checked	Checked	Checked	Checked
Muegge's	Checked	Checked	Checked	Checked	Checked
Egan's	Checked	Checked	Checked	Checked	Checked
Bioavailability Score	0.55	0.55	0.55	0.55	0.55

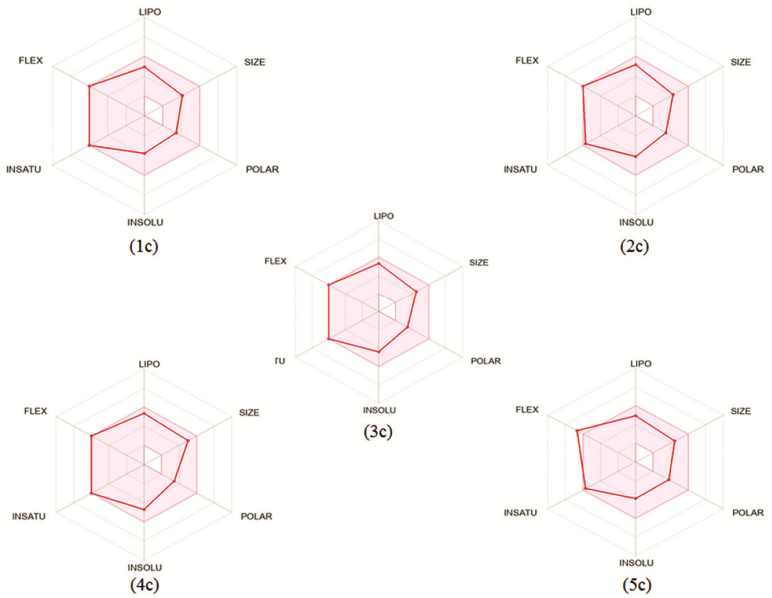


Fig. 7 — Bio-radar diagram of the synthesized five novel triazole moieties

important residue for inhibition in the case of HDAC-modified triazole moieties.

QSPR results

Skin permeability can be defined as a modest, mechanistically based model of exceptional predictivity, it approves with a lipid free-volume narrative of stratum corneum transport grounded on independent biophysical data, and lastly, the model is reliable with transport through lipid lamellae and proposes that lipid properties are alone adequate to describe stratum corneum permeability (Table 2).

Druglikeness results

The five triazole-based HDACi mimic molecules pass through all the filters of druglikeness which are Lipinski's rule of five, Ghose rule, Veber rule, and Egan rule.

The Bioavailability Score[40] calculates the possibility of a molecule having a minimum 10% oral-bioavailability measurable Caco-2 permeability in rats. It is based on a score dependent on total charge, violation of the Lipinski filter, and TPSA. It describes four modules of molecules with probabilities of 11%, 17%, 55% or 85%. It majorly emphasizes the rapid screening of drugs or lead libraries, to pick the finest molecules to be procured, synthetized, or isolated for drug discovery projects (Table 3).

The bio-radar[41,42] diagram obtained from the swissadme server is shown in Fig. 7 of all five synthesized triazole moieties.

Discussion

HDAC is extensively examined as a target for anti-cancer drug development due to its vital role in numerous biotic-biological processes like cell-proliferation, cell-metastasis, and cell-apoptosis[43]. In this study we primarily focus on the progress of simple molecules as prime compounds for drug-discovery and development based on HDACi structural feature as a Sars-Cov-2 inhibitor. Several well-known HDAC-inhibitors like vorinostat, panobinostat are clinically established. Therefore, simple moieties mimicking HDAC inhibitors targeting Sars-Cov-2 main protease, to stop their proliferation can be very useful.

The *in silico* structure activity comparison of our modified synthesized moieties tells us that the curved hydrophobic zone formed in compound 2c is important for the greater adjustment in the bonding zone of both proteins 6LU7 and 7WOP. Thus compound 2c can inhibit omicron and other future variants of Sars-Cov-2.

Conclusion

A new possibility will be opened in viral disease management through the repurposing and modification of HDACi moieties. However, a newly synthesized molecule has some shortcomings like a lot of unknown factors including drug toxicity and bioavailability, for which extensive research and time are needed. In this paper, we have designed and synthesized five inhibitors that have a triazole core and performed docking with Sars-Cov-2 main protease (M_{pro}) which shows more negative ΔG value than its co-crystalized ligand N3 and with omicron S-protein shows good binding score. The best score obtained was of compound 2c against both proteins, ΔG = − 7.4 kcal/mol for 6LU7 and − 7.3 kcal/mol for 7WOP. The druglikeness of the synthesized molecules is also good and passes through all the parameters. Thus these five inhibitors can be regarded as potential lead compounds. Despite the challenges, it can be anticipated that in the near future, the progress of simple triazole based HDACi will show a projecting role in the drug discovery and development of Sars-Cov-2 and its new variants like JN.1.

Supplementary Information

Supplementary information is available in the websitehttp://nopr.niscpr.res.in/handle/123456789/58776.

Acknowledgments

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Conflict of interest

All authors declare no conflict of interest.

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