

# De Novo Design of Potential HIV-1 Entry Inhibitors Based on the Click Chemistry Concept: A Computational Study

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One of the most attractive strategies in the current drug development is the screening of virtual compound libraries aimed at the identification of molecules with desired biological activities and drug-likeness properties. However, compounds identified in this way generally show low biological activities but can be used as good scaffolds for further optimization of their structures or as basic structures for de novo design of molecules with greater biological activity and improved pharmacokinetic properties. In this context, it seems promising to apply the methodology of click chemistry [1] that is a powerful tool for generating a large number of drug candidate structures by their assembly of small modular units. Click reactions are modular, stereospecific, wide in scope, result in high yields, and generate only safe by-products [1]. These reactions may therefore greatly simplify mass parallel synthesis of drugs candidates and accelerate the development of novel, potent and safe medications.

In this study, de novo design of potential entry inhibitor scaffolds that target CD4-binding site of the HIV-1 gp120 protein was carried out by the click reaction of azide-alkyne cycloaddition [1] followed by evaluation of their antiviral potency using high-throughput molecular docking. In the first step, a Drug-Like subset of the ZINC database

(<http://zinc.docking.org/>) was screened by the DataWarrior program (<http://www.openmolecules.org/help/basics.html>) to generate two virtual compound libraries that included small modular units with the functional groups and structural elements necessary for the design of HIV-1 inhibitor candidates within the click chemistry concept. Library 1 comprised small molecules (molecular mass <250 Da) with an azide group or an alkyne group and aromatic fragments, which provide specific ligand binding to the hydrophobic Phe43-cavity of gp120 critically important for the HIV-1 attachment to cellular receptor CD4 [2]. In library 2, all low-molecular compounds (molecular mass < 250 Da) with an azide group or an alkyne group were collected. The modular units from libraries 1 and 2 were then used as the starting reagents to mimic the reaction of azide-alkyne cycloaddition [1] by the AutoClickChem software tool ([http://nbcrc-222.ucsd.edu/autoclickchem/library\\_1.php](http://nbcrc-222.ucsd.edu/autoclickchem/library_1.php)), leading to a set of 1 655 301 hybrid molecules. 294 378 compounds that fully satisfied Lipinski's "rule of five" were further screened by high-throughput docking to evaluate the affinity of their binding to the target protein.

The Phe43 cavity of the gp120 CD4-binding site was used as the rigid receptor for flexible docking with the designed compounds by the QuickVina 2 program (<http://omictools.com/quickvina-tool>). The receptor crystal structure derived from the G chain of the gp120 core [3] was prepared by adding hydrogen atoms with the AutoDockTools software (<http://autodock.scripps.edu/resources/adt>). The cell for docking included the Phe43-cavity of gp120 and presented a fragment of the HIV-1 CD-binding site with the following coordinates:  $X \in (24 \text{ \AA}; 34 \text{ \AA})$ ,  $Y \in (-15 \text{ \AA}; -5 \text{ \AA})$ ,  $Z \in (78 \text{ \AA}; 88 \text{ \AA})$ , i.e. the volume of this cell was  $10 \times 10 \times 10 = 1000 \text{ \AA}^3$ . Parameter describing the coverage of the conformational space was set to 50. For all compounds, the docked structures with the highest scores were analyzed. The HIV-1 entry inhibitor NBD-11021 presenting a new class of full functional antagonists of cellular receptor CD4 [2] was used as a control.

As a result, six compounds were found to exhibit the lower values of the binding energy compared with the control HIV-1 inhibitor NBD-11021. These drug-like molecules were therefore identified as the potential CD4-mimetic candidates.

As an example, Figure 1 casts light on the docked ligand/gp120 structure for the compound with the best QuickVina ranking score, and Figure 2 shows the scheme of computer “synthesis” of this hybrid molecule.

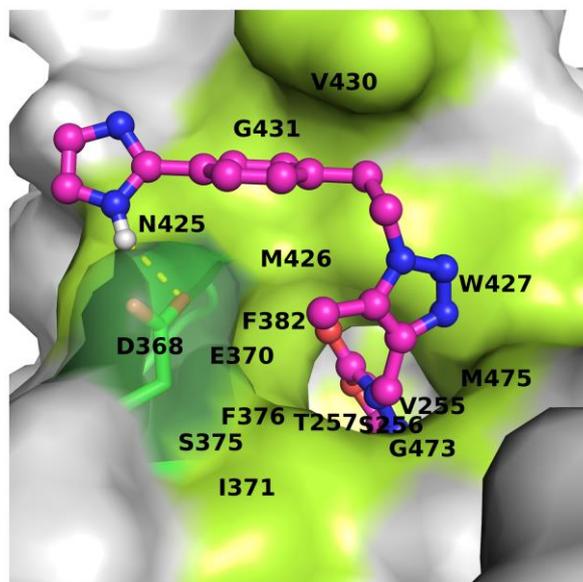


Figure 1. The docked ligand/gp120 structure for the CD4-mimetic candidate with the highest ranking score. The compound is represented by a ball-stick model. The residues of gp120 forming intermolecular contacts with the ligand are indicated. Hydrogen bond is shown by dotted line.

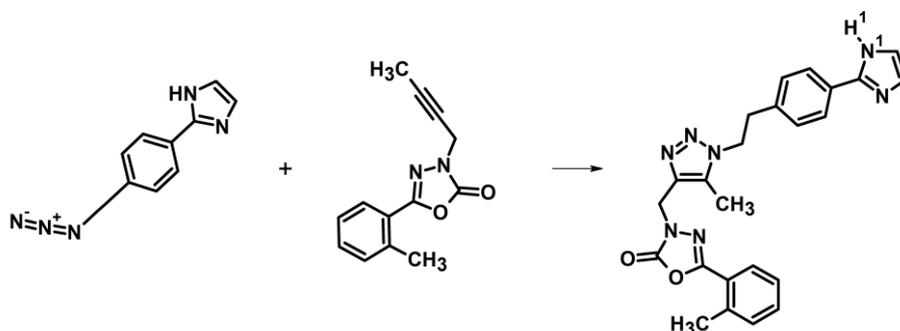


Figure 2. Scheme of computer “synthesis” of hybrid molecule with the highest ranking score. The starting reagents and final product of the reaction of azide-alkyne cycloaddition are shown. The functional group of this molecule forming hydrogen bond with Asp-368<sub>gp120</sub> is designated by superscript numerals.

Analysis of the docked structure indicates (Figure 1) that this molecule forms hydrogen bond with Asp-368<sub>gp120</sub> mimicking the critical H-bond interaction of this highly conserved gp120 residue with Arg-59<sub>CD4</sub> [3]. Along with hydrogen bond, the designed compound is involved in van der Waals interactions with the gp120 residues Asp-368, Glu-370, Ile-371, Asn-425, Met-426, Trp-427, and Gly-473 that make the direct interatomic contacts with Phe-43<sub>CD4</sub>. This observation also relates to Thr-257<sub>gp120</sub> lining under the Phe-43 ring in the crystal CD4–gp120 structure [3]. The obtained findings indicating that the predicted compound binds to Phe-43<sub>CD4</sub> and Arg-59<sub>CD4</sub> are of great interest because these residues of cellular receptor CD4 present the dominant contributors to the CD4–gp120 interface [3]. The mechanism of interactions between the other designed compounds and gp120 is close to that appearing in the docked structure shown in Figure 1. This mechanism is generally provided by hydrogen bonds with Asp-368<sub>gp120</sub> and multiple van der Waals contacts with the gp120 residues that bind to Phe-43<sub>CD4</sub>, resulting in destruction of the critical interactions of gp120 with Phe-43<sub>CD4</sub> and Arg-59<sub>CD4</sub>.

In light of these data, the predicted CD4-mimetic candidates may be used as good scaffolds for the design of new functional antagonists of viral entry with broad HIV-1 neutralization.

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### **References**

1. H.C. Kolb, M.G. Finn, K.B. Sharpless (2001) Click chemistry: Diverse chemical function from a few good reactions. *Ang. Chem. Int. Edit.*, **40**: 2004–2021.
2. F. Currelia, Y.D. Kwon, H. Zhanga et al. (2015) Structure-based design of a small molecule CD4-antagonist with broad spectrum anti-HIV-1 activity. *J. Med. Chem.*, **58**: 6909–6927.
3. Kwong P.D., Wyatt R., Robinson J., Sweet R.W., Sodroski J., Hendrickson W.A. (1998) Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature*, **393**: 648–659.