# Virtual Screening of Novel Anti-HIV-1 Agents Based on a Broadly Neutralizing Antibody VRC01 and Evaluation of Their Potential Inhibitory Activity by Molecular Docking and Dynamics Simulations

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A large number of studies published in the last few years have described the presence of anti-HIV-1 broadly neutralizing antibodies (bNAbs) in different cohorts, providing a new strategy for improved vaccine design (reviewed in [1]). There are, however, major challenges in the development of immunogens that induce bNAbs. These challenges include the extraordinary genetic diversity of the virus, the relative inaccessibility of conserved epitopes that are targeted by bNAbs, the instability of the envelope glycoprotein (Env, the only known target for neutralizing antibodies), and the difficulties encountered in sustaining NAb titers following vaccination [1]. In this connection, studies aimed at the identification of small molecules able to mimic pharmacophore properties of anti-HIV-1 bNAbs are of great interest.

In this work, computational prediction of novel HIV-1 entry inhibitors presenting peptidomimetics of potent bNAb VRC01 that partially mimics binding of the cellular receptor CD4 to gp120 was carried out based on the analysis of the X-ray complex of this antibody antigen-binding fragment with the HIV envelope gp120 core [2]. Using these empirical data, peptidomimetic candidates of bNAb VRC01 were identified by a public web-oriented virtual screening platform (pepMMsMIMIC) [3] and models of these candidates

bound to gp120 were generated by molecular docking. At the final point, the stability of the complexes of these molecules with gp120 was estimated by molecular dynamics (MD) and binding free energy calculations. The calculations identified six molecules exhibiting a high affinity to the HIV-1 gp120 protein. These molecules were selected as the most probable peptidomimetics of bNAb VRC01 (Figure 1).

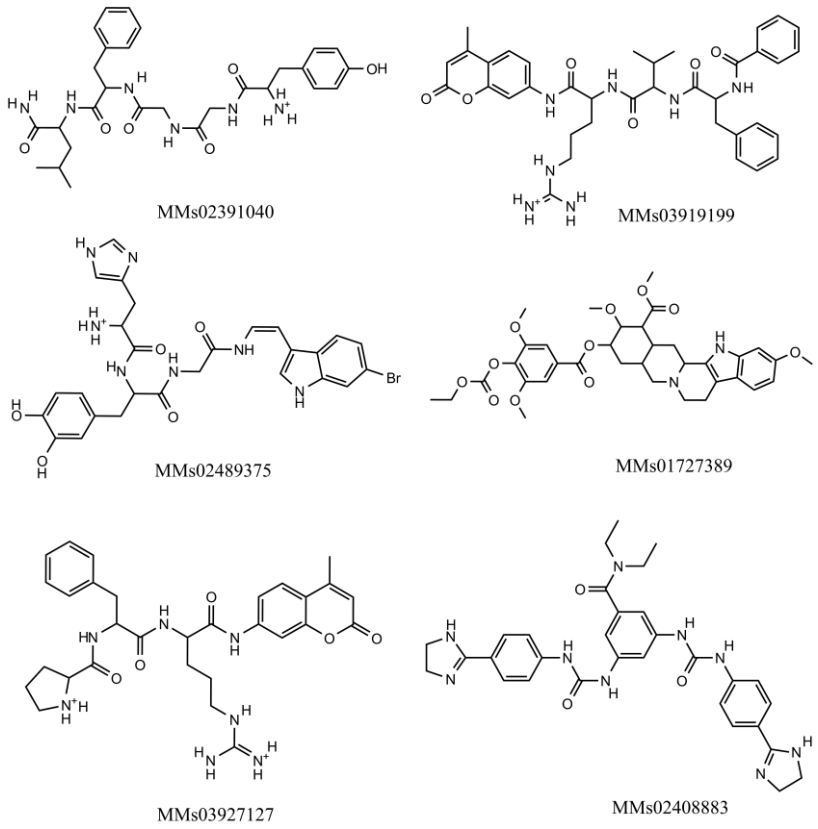


Figure 1. Two-dimensional structures of potential peptidomimetics of bNAb VRC01. The molecule codes are from the MMsINC database [4].

An insight into the docked models of the selected compounds with the gp120 core shows that these complexes exhibit intermolecular interactions involving the residues of gp120 critical for the HIV-1 binding to cellular receptor CD4. In particular, the MMs02391040, MMs03919199, MMs02489375 and MMs03927127 compounds (Figure 1) form hydrogen bonds and salt bridges with Asp-368 of gp120. These modes of interactions between Asp-

368 of gp120 and Arg-71$^{H}$ of VRC01 have been found in the X-ray structure of the antibody Fab bound to the HIV-1 gp120 core [2]. The data obtained are of interest because Asp-368 of gp120 makes critical interaction by forming a salt bridge with Arg-59 of CD4 [5]. The structural complex of MMs01727389 with gp120 shows the H-bonding between the VRC01 peptidomimetic candidate and Ser-365, Thr-455 and Gly-473 of gp120. These residues of gp120 make direct contacts both with CD4 [5] and VRC01 [2]. At the same time, Gly-473 is used by the virus for specific interactions with Phe-43 of CD4 that, along with Arg-59, is also critical for the HIV-1 binding to CD4 [5]. The MMs02408883 compound forms the four hydrogen bonds with gp120 characteristic of bNAb VRC01 [2] and participates in cation-pi interaction with Arg-456 of this glycoprotein.

Thus, the hydrogen bonds and salt bridges appearing in the analyzed complexes relate to the residues of gp120 that play an important role at the first step of the HIV-1 entry. The functionally important residues of gp120 are also involved in van der Waals interactions with the VRC01 peptidomimetics. The data obtained suggest that, in all of the cases of interest, a significant portion of these residues forms direct contacts both with CD4 and VRC01.

The MD simulations support the docking results. The MD structures of the analyzed complexes expose intermolecular hydrogen bonds involving such functionally important residues of gp120 as Asp-368 (MMs02391040, MMs03919199, MMs02489375, MMs03927127), Gly-429 (MMs02391040), Glu-370 (MMs02489375), Gly-473 (MMs01727389), Arg-456, Glu-466 and Thr-467 (MMs02408883). For the MMs02391040, MMs03927127 and MMs02408883 molecules, additional hydrogen bonds missing in the static models appear in their MD structures bound to gp120. These hydrogen bonds relate to gp120 residues Met-426 (MMs02391040), Glu-370 (MMs03927127), Asp-457 and Arg-465 (MMs02408883), which participate in the HIV-1 binding to CD4 [5]. Analysis of the MD trajectories of the docked structures also shows that the MMs02391040, MMs03919199, MMs02489375 and MMs03927127 compounds keep a salt bridge with Asp-368 of gp120 that has been found in the static models.

The complexes of the identified compounds with gp120 exhibit relative stability within the MD simulations, which is validated by the mean values of binding free energy and their standard deviations. For example, the value of binding free energy predicted for

MMs02391040 and gp120 is much lower than that of -9.5±0.1 kcal/mol, which was determined for the gp120/CD4 complex using isothermal titration calorimetry [6]. The docked structures of MMs03919199, MMs02489375, MMs03927127 and MMs02408883 with gp120 expose the binding free energies close to this experimental value.

Thus, analysis of the docked structures of MMs02391040, MMs03919199, MMs02489375, MMs01727389, MMs03927127 and MMs02408883 with gp120 shows that, similarly to VRC01, these compounds partially mimic cellular receptor CD4 by specific interactions with the functionally conserved regions of gp120 critical for the HIV-1 binding to CD4. According to the MD data, the complexes of interest do not undergo substantial rearrangements during the MD simulations, exhibiting the low values of free energy of their formation. Based on these findings, the selected compounds may be considered as promising basic structures for the rational design of novel, potent, and broad-spectrum anti-HIV-1 therapeutics.

***References***

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