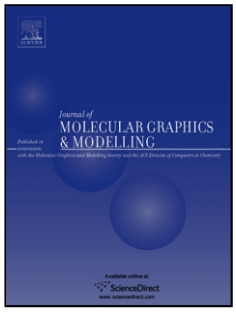

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Computational discovery of novel HIV-1 entry inhibitors based on potent and broad neutralizing antibody VRC01

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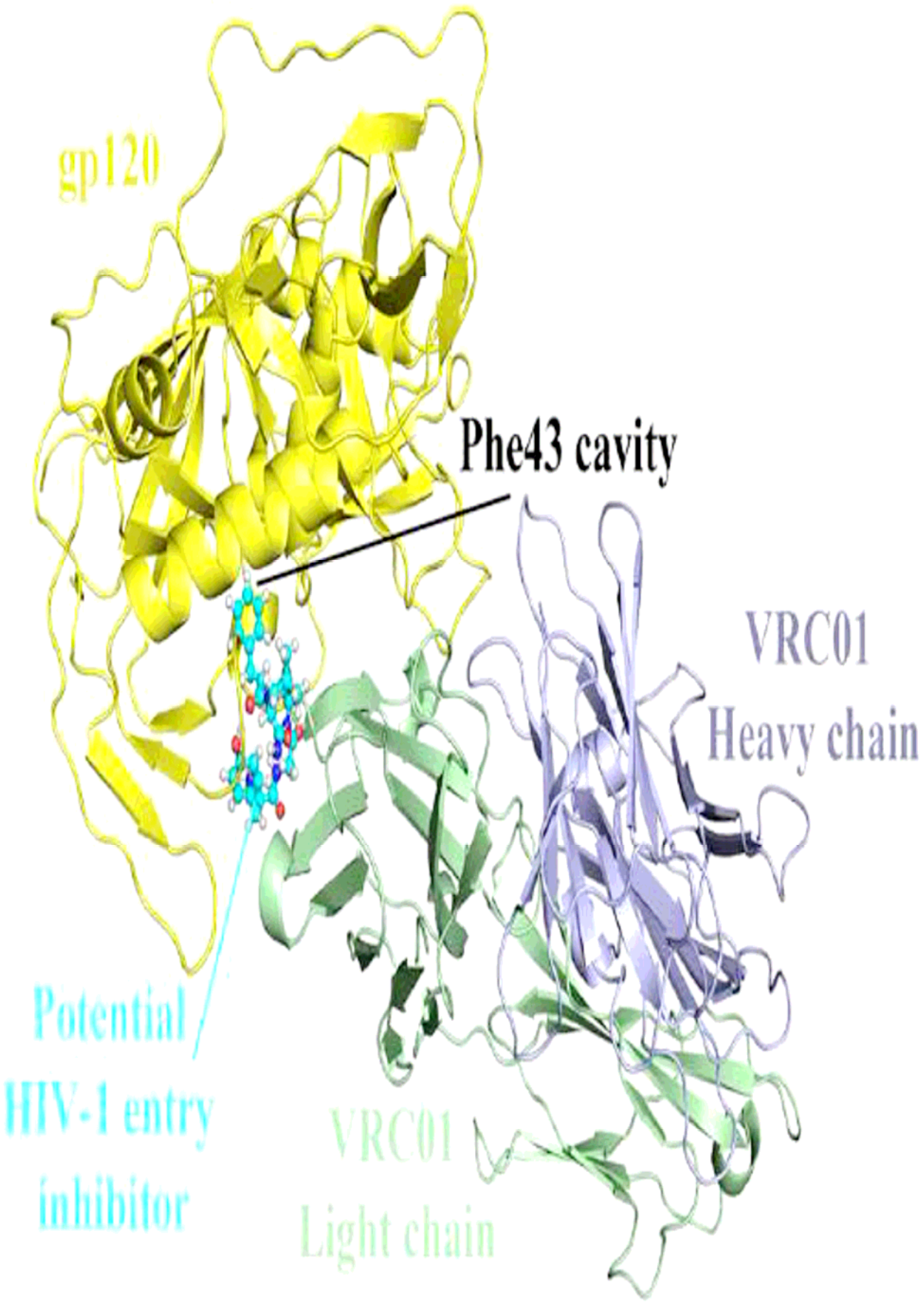
Graphical Abstract



Highlights

- Virtual screening for compounds mimicking anti-HIV-1 antibody VRC01 is performed.
- Neutralizing activity of these compounds is predicted by molecular modeling tools.
- Six small molecules are selected as the most probable peptidomimetics of VRC01.
- These molecules may be used for the design of potent and broad anti-HIV-1 drugs.

ABSTRACT

Computational prediction of novel HIV-1 entry inhibitors presenting peptidomimetics of broadly neutralizing antibody (bNAb) VRC01 was carried out based on the analysis of the X-ray complex of this antibody antigen-binding fragment with the HIV envelope gp120 core. Using these empirical data, peptidomimetic candidates of bNAb VRC01 were identified by a public web-oriented virtual screening platform (pepMMsMIMIC) 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 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. In a mechanism similar to that of bNAb VRC01, these compounds were predicted to block the functionally conserved regions of gp120 critical for the HIV-1 binding to cellular receptor CD4. The docked structures of the identified molecules with gp120 do not undergo substantial rearrangements during the molecular dynamics simulations, in agreement with the low values of free energy of their formation. Based on these findings, the selected compounds are considered as promising basic structures for the rational design of novel, potent, and broad-spectrum anti-HIV-1 therapeutics.

Keywords: HIV-1 gp120 protein; neutralizing antibody VRC01; peptidomimetics; virtual screening; molecular modeling; anti-HIV-1 therapeutics.

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is a member of the lentivirus subfamily of retroviruses. The exterior of this membrane-enveloped virus is embedded with multiple copies of gp120 and gp41, which are synthesized as a single protein precursor (gp160) and then cleaved, but remain in a noncovalent association on the membrane surface (reviewed in [1-4]). These viral antigens are involved in viral cell entry: gp120 binds to CD4 [5] and then to at least one other co-receptor on the host cell surface, before gp41-mediated fusion of the viral and target cell membranes [6, 7]. Several β-chemokine receptors have been identified as secondary viral receptors, with CXCR4 serving as the primary co-receptor for T-cell tropic (T-tropic) or T-cell line adapted (TCLA) syncytium-inducing isolates [6] and CCR5 serving as the major co-receptor for macrophage-tropic (M-tropic) non-syncytium-inducing isolates [7]. Dual-tropic viral strains, which can employ both co-receptors and, thus, are termed R5X4 viruses, have also been found [1-4].

Upon binding CD4, gp120 undergoes conformational changes that result in the formation of a stable intermediate form which binds to a secondary cellular co-receptor [8-11]. Cellular entry is mediated by rearrangements of gp41, leading to viral cell fusion [12, 13]. The secondary, tertiary, and quaternary interactions between gp120 and gp41 that are involved in their assembly have been recently determined using the cryo-EM and crystal structures of a soluble cleaved HIV-1 envelope trimer [14, 15]. Structures determined by these two independent techniques show that the trimer is relatively tightly packed, especially in gp41, but with a small opening between the envelope (Env) apex and the top of the central gp41 helices that provide the main stabilizing contact between gp41 and gp120. The gp120 subunits are held together, at least in part, by association of the V1/V2/V3 regions at the apex of the trimer. The gp120 third variable (V3) loop completes the trimer apex and forms a β-hairpin structure, as does the V3 region of monomeric gp120 [16].

Based on the understanding of viral entry, it has long been assumed that antibodies targeting functionally conserved regions of gp120 or gp41 could block viral entry and potentially prevent infection [17, 18]. Serological mapping indicated that the vaccine induced antibody response was often preferentially directed against linear epitopes on the viral Env, including the V3 loop of

gp120 [19-23]. The neutralizing antibodies against V3 are mostly type specific [24, 25] and variation within the V3 loop amino-acid sequences has been shown to occur not only between different HIV-1-infected subjects but also according to geographic location [26]. In addition, the V3 loop has also been found to be usually shielded within the trimeric structure of the viral spike and relatively inaccessible to neutralizing antibodies [27-30]. Nevertheless, the discovery of anti-HIV-1 broadly neutralizing antibodies (bNAbs) and their specific modes of recognition on the viral Env provided a new strategy for improved vaccine design (reviewed in [31-36]). There are, however, major challenges in the development of immunogens that induce bNAbs (e.g., [31, 32]). 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 [32]. Nevertheless, a large number of studies published in the last few years have described the presence of bNAbs in different cohorts [37-41]. According to these studies, neutralizing antibodies tend to increase in potency over time and broadly cross neutralizing responses, capable of recognizing heterologous HIV-1 variants, develop in a subset of individuals after primary infection. In some cases, the specificities of the antibodies conferring breadth have been mapped and are reactive with conserved envelope regions.

Advances in analyzing humoral immunity have shown that bNAbs are produced in many HIV-infected individuals [37, 39, 42], and these findings have provided hope that understanding the structure, specificity, and mechanism of their action will help to propose new approaches for vaccine design. Recent insights of ways that vaccines can potentially stimulate protective T- and B-cell immunity, the identification of new targets for bNAbs, and the discovery of new mechanisms of host control of HIV-1 bNAb induction offer a renewed hope for the development of a well tolerated and effective preventive HIV-1 vaccine [35, 36].

In light of discovering anti-HIV-1 bNAbs and their specific modes of recognition on the viral envelope, studies aimed at the identification of small molecules able to mimic pharmacophore properties of these antibodies are of great interest. In this connection, an integrated computational

approach involving theoretical procedures, such as virtual screening, molecular dynamics (MD), molecular docking, binding free energy calculations, etc. should be of great assistance in this effort. However, it is necessary to note that, although modeling techniques for computer-aided drug design are reasonably successful, there are many other properties, such as bioavailability, metabolic half-life, lack of side effects, etc., that first must be optimized before a ligand can become a safe and efficacious drug. These characteristics are often difficult to optimize by molecular modeling. In addition, all computational approaches to drug design involve various approximations. They range from simplified forms of the first-principles equations that are easier or faster to solve, to approximations limiting the size of the system (for example, periodic boundary conditions), to fundamental approximations to the underlying equations that are required to achieve any solution to them at all. Therefore, the data obtained at every stage of computer-aided drug design should be analyzed in conjunction with available experimental information.

In this work, computational prediction of novel anti-HIV-1 agents presenting potential peptidomimetics of potent and broad neutralizing antibody VRC01 [43, 44] was carried out followed by evaluation of their potential inhibitory activity using molecular modeling. The isolation and structural characterization of bNAb VRC01 showed that this antibody partially mimics binding of the cellular receptor CD4 to gp120 [43, 44]. Specifically, a region of the heavy chain of VRC01 is arranged in an anti-parallel β-sheet configuration that is similar to the interaction of domain 1 of CD4 with gp120. Structures of VRC01-like antibodies from a total of six different donors reveal a highly similar mode of recognition of the CD4-binding site [44-46]. Light chain interactions with somewhat more variable regions of V5 and the D-loop regions of gp120 explain the few cases of viral resistance to this class of bNAbs. A rather unique feature of VRC01 class antibodies is that heavy chain binding is mediated largely by CDR H2, a region encoded by the V-gene, rather than CDR H3, which is encoded by V-D-J recombination.

To reach the goal of this study, peptidomimetic candidates of bNAb VRC01 were identified by a public web-oriented virtual screening platform (pepMMsMIMIC) [47] 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 MD and binding free energy calculations.

As a result, the calculations identified six molecules exhibiting a high affinity to the HIV-1 gp120 protein. These molecules were predicted to present promising basic structures for the rational design of novel, potent, and broad-spectrum anti-HIV-1 therapeutics.

2. Materials and methods

The first step of the pepMMsMIMIC strategy consists in the identification of the key residues that are responsible for the protein-protein recognition process [47]. In this step, all possible combinations of these residues exhibiting critical structural features in three-dimensional space may be used for generation of the input dataset to screen virtual compound libraries for novel ligands, which present the best similarity to the specific pharmacophore [47]. Based on this strategy, thirteen residues of the VRC01 antigen-binding fragment (Fab) forming hydrogen bonds with the gp120 core in the X-ray complex [44] were used as the basic pharmacophore model for search of the most probable peptidomimetics of this antibody. To identify small-molecule peptidomimetic candidates, seven short fragments of this model that bind to different critical regions of the CD4-binding site of gp120 were used as the additional input data for pepMMsMIMIC. When designing these fragments, VRC01 residues Trp47, Tyr74 and Phe97 that do not participate in the hydrogen bonding with gp120 [44] but form the antibody binding hotspots [48] were also taken into consideration. The final input dataset obtained in this way comprised eight pharmacophore models describing different structural elements of the VRC01 Fab (Table 1).

The search for peptidomimetics was performed using four different scoring methods that are implemented in the current version of pepMMsMIMIC [47] associated with the MMsINC database (http://mms.dsfarm.unipd.it/MMsINC.html) [49]. The database contains 17 million conformers calculated from 3.9 million commercially available chemicals. The tools offer five search procedures and different combinations of two scoring approaches, such as ultrafast shape recognition [50] and pharmacophore fingerprints similarity [51, 52]. The resulting ensemble of

peptidomimetic candidates found in the MMsINC database was then evaluated by molecular docking to assess the efficacy of their binding to the HIV-1 gp120 core.

The 3D structure of gp120 was extracted from its X-ray complex with the bNAb VRC01 Fab (code 3NGB in the Protein Data Bank; http://www.rcsb.org/pdb/) [44] and used as rigid receptor for flexible ligand docking with ensembles from the MMsINC database using the AutoDock VINA program [53]. Hydrogen atoms were added to the X-ray gp120 structure by the AutoDockTools package (http://autodock.scripps.edu/resources/adt) [53]. For all peptidomimetic candidates, the structural complexes with the highest scores were analyzed to identify the compounds that, similarly to VRC01, specifically and effectively interact with the CD4-binding site of gp120. Based on the AutoDock VINA scoring function, the docked structures of 20 top-scoring compounds with gp120 were selected to be subject to MD and binding free energy calculations.

The MD simulations were carried out by the Amber 11 computer package using the Amber ff10 force field [54]. The ligand parameters were obtained with the generalized Amber force field (GAFF) approach [55]. The initial coordinates of the gp120 hydrogen atoms were determined by the xleap program of the AMBER 11 package [54]. The docked structure was placed in a truncated octahedron box with walls at least 10 Å from the nearest structural atoms, filled with TIP3P water [56] as an explicit solvent, and subjected to periodic boundary conditions. The system was prepared for MD simulation by 500 steps of steepest descent method followed by 1000 steps of conjugate gradient energy minimization. The following convergence criterion for the energy gradient was used: minimization halted when the root-mean-square of the Cartesian elements of the gradient was less than 10^{-4} kcal/mole-Å [54]. The atoms of the complex assembly were then restrained by an additional harmonic potential with the force constant equal to 1.0 kcal/mol and then heated from 0 to 310 K over 1 ns using a constant volume of the unit cell. Additional equilibration was performed over 1 ns by setting the system pressure to 1.0 atm and by using a weak coupling of the system temperature to a 310 K bath [57] with a 2.0 ps characteristic time. Finally, the constraints on the complex assembly were removed and the system was equilibrated again at 310 K over 2 ns under constant volume conditions. After equilibration, the isothermal-

isobaric MD simulation (T = 310 K, P = 1.0 atm) generated 30 ns trajectory using a Berendsen barostat with a 2.0 ps characteristic time, a Langevin thermostat with collision frequency 2.0 ps^{-1}, a non-bonded cut-off distance of 8 Å, and a simple leapfrog integrator [54] with a 2.0 fs time step and bonds with hydrogen atoms constrained by the SHAKE algorithm [58]. Electrostatic interactions were calculated at every step with the particle-mesh Ewald method [59], short-range repulsive and attractive dispersion interactions were simultaneously described by a Lennard-Jones potential.

The free energy of binding was used as a measure of conformational stability of the complexes of interest and was calculated by the MM-PB/SA procedure [60] in AMBER 11 [54]. Five hundred snapshots were selected from the last 25 ns to estimate the binding free energy, by keeping the snapshots every 50 ps. The polar solvation energies were computed in continuum solvent using Poisson-Boltzmann and ionic strength of 0.1. The non-polar terms were estimated using solvent accessible surface areas [61].

Hydrogen bonds, salt bridges and cation-pi interactions between the selected compounds and gp120 were analyzed by the BINANA program [62]. The ptraj procedure associated with AMBER 11 [54] was used to identify hydrogen bonds in the dynamic models of these structures. The hydrogen bond was defined by the acceptor and the hydrogen atom. A hydrogen bond was considered to be formed if the hydrogen–acceptor distance was ≤ 3.0 Å and the donor–hydrogen–acceptor angle was >120°. Van der Waals contacts between the VRC01 peptidomimetic candidates and gp120 were determined with the use of the program Ligplot [63].

All calculations were run on the SKIF-UIIP computer cluster [64].

3. Results and discussion

Using the input data set (Table 1), the pepMMsMIMIC tools [47] identified 4282 peptidomimetic candidates from the MMsINC database [49]. The MD simulations of the twenty top-ranking docked complexes between the VRC01 potential peptidomimetics and gp120 revealed six molecules that exposed negative binding free energy values. These molecules were therefore

selected for the final analyses. Brief information on these compounds is cited in Table 2 and their two-dimensional structures derived from MMsINC [49] are shown in Figure 1.

Visualization of the docked models of the selected compounds with the gp120 core indicates (Table 3) 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 form hydrogen bonds and salt bridges with Asp-368 of gp120 (Table 3). 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 [44]. The data obtained are of interest because Asp-368 of gp120 makes critical interaction by forming a salt bridge with Arg-59 of CD4 [65]. 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 (Table 3). These residues of gp120 make direct contacts both with CD4 [65] and VRC01 [44]. 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 [65]. The MMs02408883 compound forms the four hydrogen bonds with gp120 (Table 3) characteristic of bNAb VRC01 [44] and participates in cation-pi interaction with Arg-456 of this glycoprotein.

Thus, the hydrogen bonds and salt bridges appearing in the analyzed complexes (Table 3) 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 (Table 4). The data given in Table 4 suggest that, in all of the cases of interest, a significant portion of these residues forms direct contacts both with CD4 and VRC01.

Analysis of the docked structures of the selected compounds with gp120 illustrates (Figure 2) that the MMs02391040, MMs03919199, MMs02489375, MMs01727389 and MMs03927127 compounds target the Phe-43 cavity of gp120. It is known that this site of gp120 promotes the HIV-1 attachment to target cell by specific interactions of its amino acids Glu-370, Ile-371, Asn-425, Met-426, Trp-427, and Gly-473 with Phe-43 of CD4 [65]. As shown in Figure 2, a-e, one of

the aromatic rings of these compounds (Figure 1) is buried into the Phe-43 cavity, resulting in the masking of the above residues of gp120. For example, phenylalanine of the MMs02391040 compound (Figure 1) blocking these gp120 amino acids (Figure 2, a) actually mimics Phe-43 of CD4, which, obviously, should prevent HIV-1 from the binding to host cell.

As opposed to the above molecules bound to the Phe-43 cavity of gp120 (Figure 2, a-e), the MMs02408883 compound partially covers the D-loop and the V5/β24 region of gp120 (Figure 2, f). This compound forms hydrogen bonds with gp120 residues Asn-280 (D-loop), Arg-456 (V5 loop), Glu-466 and Thr-467 (β24-segment) (Table 3), which are also seen to interact with VRC01 [44]. In addition, MMs02408883 makes the van der Waals contacts with a number of the gp120 amino acids that are involved in the binding to VRC01 and CD4 (Table 4).

Figure 3 casts light on the superimposed complexes of the HIV-1 gp120 core with the VRC01 Fab and peptidomimetic candidates. The VRC01 Fab interacts with gp120 using both light and heavy chains (Figure 3) [44]. The primary interaction surface of VRC01 is provided by the CDR H2 region, with the CDR L1 and L3 and the CDR H1 and H3 providing additional contacts [44]. The identified compounds partially mask the region of gp120 that is targeted by VRC01, forming much less contact surface with gp120 as compared to this antibody (Figure 3). Nevertheless, these small molecules bind to the vulnerable spots of this gp120 region and may therefore exhibit the functional mimicry of VRC01. Analysis of Figure 3 shows that the MMs02391040, MMs03919199, MMs02489375, MMs01727389 and MMs03927127 compounds mimic segment Arg-53–Gly-54–Gly-55 of the VRC01 critical region CDR H2 blocking the Phe-43 cavity of gp120 (Figure 3). Similarly to VRC01 [44], these compounds also mimic the arginine interaction with Asp-368 of gp120 (Table 3) that is crucial for the HIV-1 binding to CD4 [65]. The MMs02408883 compound targeting the V5/β24/D-loop site of gp120 (Figure 2, f) imitates the fragments both of the heavy and light chains of VRC01 that include residues Arg-61 (CDR H2 region), Tyr-91 and Glu-96 (CDR L3 region) (Figure 3).

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) (Table 3). For the MMs02391040, MMs03927127 and MMs02408883 molecules, additional hydrogen bonds missing in the static models appear in their MD structures bound to gp120 (Table 3). As follows from Table 3, 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 [65]. 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 (Table 3).

Figure 4 shows the variations in the root-mean square deviations (RMSD) of the atomic coordinates of the gp120/peptidomimetic complexes from those appearing in the first structures of the MD trajectories. As follows from Figure 4, these complexes do not go through considerable structural changes during the 25 ns time domain. The averages of the RMSD change from 1.69± 0.20 Å (the MMs03919199/gp120 complex) to 2.24±0.48 Å (the MMs02489375/gp120 complex). At the same time, comparison of the MD structures between themselves results in approximately the same mean values of RMSD varying from 1.54±0.28 Å (MMs01727389/gp120) to 1.95±0.42 Å (MMs02408883/gp120). The averages of the RMSDs close to the above values were also obtained for gp120 and for peptidomimetic candidates in the bound forms by comparing their MD structures both with the starting points and each other.

Thus, the complexes of interest and their constituents exhibit relative stability within the MD simulations, which is validated by the mean values of binding free energy and their standard deviations (Table 5). The value of binding free energy predicted for MMs02391040 and gp120 (Table 5) is much lower than that of -9.5±0.1 kcal/mol, which was determined for the gp120/CD4 complex using isothermal titration calorimetry [66]. The docked structures of MMs03919199,

MMs02489375, MMs03927127 and MMs02408883 with gp120 exhibit the binding free energies close to this experimental value (Table 5).

4. Conclusions

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 (Figure 2). 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 (Table 5).

Thus, the molecular modeling data clearly suggest that the chemical compounds found in the MMsINC database (Figure 1) may be able to neutralize different HIV-1 modifications. It is clear that the final confirmation of these data may be obtained only after testing the identified compounds for anti-HIV-1 activity against various viral isolates. This study is now in progress and its further advancement proposes to use these VRC01 peptidomimetic candidates as the fixed scaffolds for computer-based generation of their modified forms with improved antiviral potency and drug-like properties (e.g., [67, 68]) followed by synthesis and anti-HIV activity assays. The molecules of interest are most likely to be capable of neutralizing HIV-1 virions only on surface of the target cell via blocking the virus attachment to cellular receptor CD4. To enhance HIV-1 inactivation, these molecules may be combined with different anti-HIV agents targeting the viral vulnerable spots distinct from CD4-binding site of gp120. In particular, a computational approach used here has been recently applied to the search for potential peptidomimetics of anti-HIV-1 bNAb 10E8 (preliminary communication [69]) neutralizing up to 98% of diverse HIV-1 strains by specific interactions with the membrane-proximal external region of the envelope protein gp41 [70]. As a result, eight chemical compounds from MMsINC were shown to exhibit a high affinity to this gp41 site [69] critical for Env-mediated fusion and virus infectivity [70, 71]. In this context, we suppose that a bifunctional anti-HIV-1 “cocktail” of small-molecule peptidomimetics of bNAbs VRC01 and 10E8 may suppress viral replication and reduce the plasma HIV-1 viral load.

A bivalent HIV-1 antagonist 2DLT [72] targeting the gp41 prehairpin fusion intermediate induced by CD4 D1D2 domains is an example of novel potent HIV-1 inhibitor that prevents the HIV-1 binding to CD4 and fusion of the virus with a cell membrane. At the same time, 2DLT acts as a dual barrier against HIV infection by first inactivating HIV-1 virions away from cells and then blocking HIV-1 entry on the target cell surface [72]. Synergistic effect resulting from combinations of this bifunctional recombinant protein with different antiretroviral drugs has been observed in a study [73].

So analysis of the data obtained indicates that the VRC01 peptidomimetics shown in Figure 1 provide promising scaffolds for the development of novel small molecule drugs to neutralize HIV-1.

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References

[1] O. Hartley, P.J. Klasse, Q.J. Sattentau, J.P. Moore, V3: HIV's switch-hitter, AIDS Res. Hum. Retroviruses 21 (2005) 171–189. doi:10.1089/aid.2005.21.171.

[2] S. Sirois, T. Sing, K.-C. Chou, HIV-1 gp120 V3 loop for structure-based drug design, Curr. Protein Pept. Sci. 6 (2005) 413–422. PMID: 16248793.

[3] S. Sirois, M. Touaibia, K.-C. Chou, R. Roy, Glycosylation of HIV-1 gp120 V3 loop: towards the rational design of a synthetic carbohydrate vaccine, Curr. Med. Chem. 14 (2007) 3232–3242. doi:10.2174/092986707782793826.

[4] A.M. Andrianov, Human immunodeficiency virus-1 gp120 V3 loop for anti-acquired immune deficiency syndrome drug discovery: computer-aided approaches to the problem solving, Expert Opin. Drug Discov. 6 (2011) 419–435. doi:10.1517/17460441.2011.560603.

[5] A.G. Dalgleish, P.C. Beverley, P.R. Clapham, D.H. Crawford, M.F. Greaves, R.A. Weiss, The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus, Nature 312 763–767. http://www.ncbi.nlm.nih.gov/pubmed/6096719 (accessed February 21, 2015).

[6] Y. Feng, C.C. Broder, P.E. Kennedy, E.A. Berger, HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor, Science 272 (1996) 872–877. doi:10.1126/science.272.5263.872.

[7] F. Cocchi, A.L. DeVico, A. Garzino-Demo, A. Cara, R.C. Gallo, P. Lusso, The V3 domain of the HIV-1 gp120 envelope glycoprotein is critical for chemokine-mediated blockade of infection, Nat. Med. 2 (1996) 1244–1247. doi:10.1038/nm1196-1244.

[8] E.A. Berger, P.M. Murphy, J.M. Farber, Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease, Annu. Rev. Immunol. 17 (1999) 657–700. doi:10.1146/annurev.immunol.17.1.657.

[9] L. Wu, N.P. Gerard, R. Wyatt, H. Choe, C. Parolin, N. Ruffing, et al., CD4-induced interaction of primary HIV-1 gp120 glycoproteins with the chemokine receptor CCR-5, Nature 384 (1996) 179–183. doi:10.1038/384179a0.

[10] T. Dragic, V. Litwin, G.P. Allaway, S.R. Martin, Y. Huang, K.A. Nagashima, et al., HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5, Nature 381 (1996) 667–673. doi:10.1038/381667a0.

[11] H. Deng, R. Liu, W. Ellmeier, S. Choe, D. Unutmaz, M. Burkhart, et al., Identification of a major co-receptor for primary isolates of HIV-1, Nature 381 (1996) 661–666. doi:10.1038/381661a0.

[12] R. Wyatt, J. Sodroski, The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens, Science 280 (1998) 1884–1888. doi:10.1126/science.280.5371.1884.

[13] K. Salzwedel, E.A. Berger, Cooperative subunit interactions within the oligomeric envelope glycoprotein of HIV-1: functional complementation of specific defects in gp120 and gp41, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 12794–12799. doi:10.1073/pnas.230438497.

[14] D. Lyumkis, J.-P. Julien, N. de Val, A. Cupo, C.S. Potter, P.-J. Klasse, et al., Cryo-EM structure of a fully glycosylated soluble cleaved HIV-1 envelope trimer, Science 342 (2013) 1484–1490. doi:10.1126/science.1245627.

[15] J.-P. Julien, A. Cupo, D. Sok, R.L. Stanfield, D. Lyumkis, M.C. Deller, et al., Crystal structure of a soluble cleaved HIV-1 envelope trimer, Science 342 (2013) 1477–1483. doi:10.1126/science.1245625.

[16] C. Huang, M. Tang, M.-Y. Zhang, S. Majeed, E. Montabana, R.L. Stanfield, et al., Structure of a V3-containing HIV-1 gp120 core, Science 310 (2005) 1025–1028. doi:10.1126/science.1118398.

[17] R.A. Weiss, P.R. Clapham, J.N. Weber, A.G. Dalgleish, L.A. Lasky, P.W. Berman, Variable and conserved neutralization antigens of human immunodeficiency virus, Nature 324 (1986) 572–575. doi:10.1038/324572a0.

[18] R. Shibata, T. Igarashi, N. Haigwood, A. Buckler-White, R. Ogert, W. Ross, et al., Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infections of macaque monkeys, Nat. Med. 5 (1999) 204–210. doi:10.1038/5568.

[19] T.J. Palker, M.E. Clark, A.J. Langlois, T.J. Matthews, K.J. Weinhold, R.R. Randall, et al., Type-specific neutralization of the human immunodeficiency virus with antibodies to env-encoded synthetic peptides, Proc. Natl. Acad. Sci. U. S. A. 85 (1988) 1932–1936. doi:10.1073/pnas.85.6.1932.

[20] K. Javaherian, A.J. Langlois, C. McDanal, K.L. Ross, L.I. Eckler, C.L. Jellis, et al., Principal neutralizing domain of the human immunodeficiency virus type 1 envelope protein, Proc. Natl. Acad. Sci. U. S. A. 86 (1989) 6768–6772.

[21] J. Goudsmit, C. Debouck, R.H. Meloen, L. Smit, M. Bakker, D.M. Asher, et al., Human immunodeficiency virus type 1 neutralization epitope with conserved architecture elicits early type-specific antibodies in experimentally infected chimpanzees, Proc. Natl. Acad. Sci. U. S. A. 85 (1988) 4478–4482. doi:10.1073/pnas.85.12.4478.

[22] T.C. VanCott, J.R. Mascola, L.D. Loomis-Price, F. Sinangil, N. Zitomersky, J. McNeil, et al., Cross-subtype neutralizing antibodies induced in baboons by a subtype E gp120 immunogen based on an R5 primary human immunodeficiency virus type 1 envelope, J. Virol. 73 (1999) 4640–4650.

[23] T.C. VanCott, J.R. Mascola, R.W. Kaminski, V. Kalyanaraman, P.L. Hallberg, P.R. Burnett, et al., Antibodies with specificity to native gp120 and neutralization activity against primary human immunodeficiency virus type 1 isolates elicited by immunization with oligomeric gp160, J. Virol. 71 (1997) 4319–4330.

[24] D.J. Looney, A.G. Fisher, S.D. Putney, J.R. Rusche, R.R. Redfield, D.S. Burke, et al., Type-restricted neutralization of molecular clones of human immunodeficiency virus, Science 241 (1988) 357–359. doi:10.1126/science.3388046.

[25] R.H. Meloen, R.M. Liskamp, J. Goudsmit, Specificity and function of the individual amino acids of an important determinant of human immunodeficiency virus type 1 that induces neutralizing activity, J. Gen. Virol. 70 (Pt 6) (1989) 1505–1512.

[26] Human Retroviruses and AIDS 1993: A Compilation and Analysis of Nucleic Acid and Amino Acid Sequences, G. Myers, B. Korber, S. Wain-Hobson, R.F. Smith, Eds. Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM.

[27] T.J. Matthews, Dilemma of neutralization resistance of HIV-1 field isolates and vaccine development, AIDS Res. Hum. Retroviruses 10 (1994) 631–632. http://www.ncbi.nlm.nih.gov/pubmed/8074926 (accessed April 4, 2015).

[28] X. Wu, A. Sambor, M.C. Nason, Z.Y. Yang, L. Wu, S. Zolla-Pazner, et al., Soluble CD4 broadens neutralization of V3-directed monoclonal antibodies and guinea pig vaccine sera against HIV-1 subtype B and C reference viruses, Virology 380 (2008) 285–295. doi:10.1016/j.virol.2008.07.007.

[29] J.M. Binley, T. Wrin, B. Korber, M.B. Zwick, M. Wang, C. Chappey, et al., Comprehensive cross-clade neutralization analysis of a panel of anti-human immunodeficiency virus type 1 monoclonal antibodies, J. Virol. 78 (2004) 13232–13252. doi:10.1128/JVI.78.23.13232-13252.2004.

[30] T.C. Vancott, V.R. Polonis, L.D. Loomis, N.L. Michael, P.L. Nara, D.L. Birx, Differential role of V3-specific antibodies in neutralization assays involving primary and laboratory-adapted isolates of HIV type 1, AIDS Res. Hum. Retroviruses 11 (1995) 1379–1391. http://www.ncbi.nlm.nih.gov/pubmed/8573396 (accessed April 4, 2015).

[31] J.A. Hoxie, Toward an antibody-based HIV-1 vaccine, Annu. Rev. Med. 61 (2010) 135–152. doi:10.1146/annurev.med.60.042507.164323.

[32] L.M. Walker, D.R. Burton, Rational antibody-based HIV-1 vaccine design: Current approaches and future directions, Curr. Opin. Immunol. 22 (2010) 358–366. doi:10.1016/j.coi.2010.02.012.

[33] P.D. Kwong, J.R. Mascola, G.J. Nabel, Rational design of vaccines to elicit broadly neutralizing antibodies to HIV-1, Cold Spring Harb. Perspect. Med. 1 (2011). doi:10.1101/cshperspect.a007278.

[34] L.E. McCoy, R. A. Weiss, Neutralizing antibodies to HIV-1 induced by immunization, J. Exp. Med. 210 (2013) 209–223. doi:10.1084/jem.20121827.

[35] J.R. Mascola, B.F. Haynes, HIV-1 neutralizing antibodies: understanding nature's pathways, Immunol. Rev. 254 (2013) 225–244. doi:10.1111/imr.12075.

[36] B.F. Haynes, M.J. McElrath, Progress in HIV-1 vaccine development, Curr. Opin. HIV AIDS 8 (2013) 326–332. doi:10.1097/COH.0b013e328361d178.

[37] J.M. Binley, E.A. Lybarger, E.T. Crooks, M.S. Seaman, E. Gray, K.L. Davis, et al., Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C, J. Virol. 82 (2008) 11651–11668. doi:10.1128/JVI.01762-08.

[38] A. Piantadosi, D. Panteleeff, C.A. Blish, J.M. Baeten, W. Jaoko, R.S. McClelland, et al., Breadth of neutralizing antibody response to human immunodeficiency virus type 1 is affected by factors early in infection but does not influence disease progression, J. Virol. 83 (2009) 10269–10274. doi:10.1128/JVI.01149-09.

[39] D.N. Sather, J. Armann, L.K. Ching, A. Mavrantoni, G. Sellhorn, Z. Caldwell, et al., Factors associated with the development of cross-reactive neutralizing antibodies during human immunodeficiency virus type 1 infection, J. Virol. 83 (2009) 757–769. doi:10.1128/JVI.02036-08.

[40] M.D. Simek, W. Rida, F.H. Priddy, P. Pung, E. Carrow, D.S. Laufer, et al., Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm, J. Virol. 83 (2009) 7337–7348. doi:10.1128/JVI.00110-09.

[41] E.S. Gray, M.C. Madiga, T. Hermanus, P.L. Moore, C.K. Wibmer, N.L. Tumba, et al., The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection, J. Virol. 85 (2011) 4828–4840. doi:10.1128/JVI.00198-11.

[42] J.F. Scheid, H. Mouquet, N. Feldhahn, M.S. Seaman, K. Velinzon, J. Pietzsch, et al., Broad diversity of neutralizing antibodies isolated from memory B cells in HIV-infected individuals, Nature 458 (2009) 636–640. doi:10.1038/nature07930.

[43] X. Wu, Z.-Y. Yang, Y. Li, C.-M. Hogerkorp, W.R. Schief, M.S. Seaman, et al., Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1, Science 329 (2010) 856–861. doi:10.1126/science.1187659.

[44] T. Zhou, I. Georgiev, X. Wu, Z.-Y. Yang, K. Dai, A. Finzi, et al., Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01, Science 329 (2010) 811–817. doi:10.1126/science.1192819.

[45] X. Wu, T. Zhou, J. Zhu, B. Zhang, I. Georgiev, C. Wang, et al., Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing, Science 333 (2011) 1593–1602. doi:10.1126/science.1207532.

[46] R. Diskin, J.F. Scheid, P.M. Marcovecchio, A.P. West, F. Klein, H. Gao, et al., Increasing the potency and breadth of an HIV antibody by using structure-based rational design, Science 334 (2011) 1289–1293. doi:10.1126/science.1213782.

[47] M. Floris, J. Masciocchi, M. Fanton, S. Moro, Swimming into peptidomimetic chemical space using pepMMsMIMIC, Nucleic Acids Res. 39 (2011) W261–W269. doi:10.1093/nar/gkr287.

[48] Y. Zhang, D. Pan, Y. Shen, N. Jin, H. Liu, X. Yao, Understanding the molecular mechanism of the broad and potent neutralization of HIV-1 by antibody VRC01 from the perspective of molecular dynamics simulation and binding free energy calculations, J. Mol. Model. 18 (2012) 4517–4527. doi:10.1007/s00894-012-1450-z.

[49] J. Masciocchi, G. Frau, M. Fanton, M. Sturlese, M. Floris, L. Pireddu, et al., MMsINC: a large-scale chemoinformatics database, Nucleic Acids Res. 37 (2009) D284–D290. doi:gkn727 [pii]\n10.1093/nar/gkn727.

[50] P.J. Ballester, W.G. Richards, Ultrafast shape recognition to search compound databases for similar molecular shapes, J. Comput. Chem. 28 (2007) 1711–1723. doi:10.1002/jcc.20681.

[51] J.S. Mason, I. Morize, P.R. Menard, D.L. Cheney, C. Hulme, R.F. Labaudiniere, New 4-point pharmacophore method for molecular similarity and diversity applications: overview of the method and applications, including a novel approach to the design of combinatorial libraries containing privileged substructures, J. Med. Chem. 42 (1999) 3251–3264. doi:10.1021/jm9806998.

[52] T. Langer, R.D. Hoffmann, eds., Pharmacophores and Pharmacophore Searches, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, 2006. doi:10.1002/3527609164.

[53] O. Trott, A.J. Olson, Software news and update AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J. Comput. Chem. 31 (2010) 455–461. doi:10.1002/jcc.21334.

[54] D.A. Case, T.A. Darden, I.I.I. Cheatham T.E., C.L. Simmerling, J. Wang, R.E. Duke, et al., AMBER 11, Univ. California, San Fr. (2010).

[55] J. Wang, R.M. Wolf, J.W. Caldwell, P.A. Kollman, D.A. Case, Development and testing of a general Amber force field, J. Comput. Chem. 25 (2004) 1157–1174. doi:10.1002/jcc.20035.

[56] W.L. Jorgensen, J. Chandrasekhar, J.D. Madura, R.W. Impey, M.L. Klein, Comparison of simple potential functions for simulating liquid water, J. Chem. Phys. 79 (1983) 926–935. doi:10.1063/1.445869.

[57] H.J.C. Berendsen, J.P.M. Postma, W.F. van Gunsteren, A. DiNola, J.R. Haak, Molecular dynamics with coupling to an external bath, J. Chem. Phys. 81 (1984) 3684–3690. doi:10.1063/1.448118.

[58] J.P. Ryckaert, G. Ciccotti, H.J.C. Berendsen, Numerical integration of the Cartesian equations of motion of a system with constraints: molecular dynamics of n-alkanes, J. Comput. Phys. 23 (1977) 327–341. doi:10.1016/0021-9991(77)90098-5.

[59] U. Essmann, L. Perera, M.L. Berkowitz, T. Darden, H. Lee, L.G. Pedersen, A smooth particle mesh Ewald method, J Chem Phys. 103 (1995) 8577–8593. doi:10.1063/1.470117.

[60] I. Massova, P.A. Kollman, Computational alanine scanning to probe protein-protein interactions: A novel approach to evaluate binding free energies, J. Am. Chem. Soc. 121 (1999) 8133–8143. doi:10.1021/ja990935j.

[61] K. Lindorff-Larsen, S. Piana, K. Palmo, P. Maragakis, J.L. Klepeis, R.O. Dror, et al., Improved side-chain torsion potentials for the Amber ff99SB protein force field, Proteins: Struct. Funct. Bioinform. 78 (2010) 1950–1958. doi:10.1002/prot.22711.

[62] J.D. Durrant, J.A. McCammon, BINANA: A novel algorithm for ligand-binding characterization, J. Mol. Graph. Model. 29 (2011) 888–893. doi:10.1016/j.jmgm.2011.01.004.

[63] I.K. McDonald, J.M. Thornton, Satisfying hydrogen bonding potential in proteins, J. Mol. Biol. 238 (1994) 777–793. doi:10.1006/jmbi.1994.1334.

[64] S.V. Ablameyko, U.V. Anishchanka, S.V. Medvedev, N.N. Paramonov, O.P. Tchij, SKIF Supercomputer Configurations United Institute of Informatics Problems, Minsk, (2005).

[65] P.D. Kwong, R. Wyatt, J. Robinson, R.W. Sweet, J. Sodroski, W.A. Hendrickson, Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody, Nature 393 (1998) 648–659. doi:10.1038/31405.

[66] D.G. Myszka, R.W. Sweet, P. Hensley, M. Brigham-Burke, P.D. Kwong, W.A. Hendrickson, et al., Energetics of the HIV gp120-CD4 binding reaction, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 9026–9031. doi:10.1073/pnas.97.16.9026.

[67] J.D. Durrant, R. E. Amaro, J.A. McCammon, AutoGrow: a novel algorithm for protein inhibitor design, Chem. Biol. Drug. Des. 73 (2009) 168–178. doi: 10.1111/j.1747-0285.2008.00761.x.

[68] J.D. Durrant, S. Lindert, J.A. McCammon, AutoGrow 3.0: an improved algorithm for chemically tractable, semi-automated protein inhibitor design, J. Mol. Graph. Model. 44 (2013) 104–112. doi: 10.1016/j.jmgm.2013.05.006.

[69] I.A. Kashyn, A.V. Tuzikov, A.M. Andrianov, Computer-based screening of small-molecule HIV-1 entry inhibitors based on neutralizing antibody 10E8, Doklady Natl. Acad. Sci. Belarus (in Russian) 59, N 3 (2015) 56–65. ISSN 0002-354X.

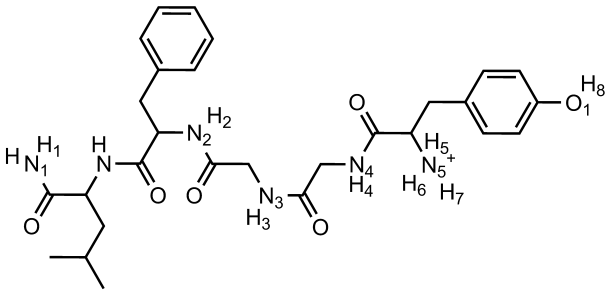
[70] J. Huang, G. Ofek, L. Laub, M.K. Louder, N.A. Doria-Rose, N.S. Longo, H. Imamichi, R.T. Bailer, B. Chakrabarti, S.K. Sharma, S.M. Alam, T. Wang, Y. Yang, B. Zhang, S.A. Migueles, R. Wyatt, B.F. Haynes, P.D. Kwong, J.R. Mascola, M Connors, Broad and potent neutralization of HIV-1 by a gp41-specific human antibody, Nature 491 (2012) 406–412. doi: 10.1038/nature11544.

[71] I. Munoz-Barroso, K. Salzwedel, E. Hunter, R. Blumenthal, Role of the membrane-proximal domain in the initial stages of human immunodeficiency virus type 1 envelope glycoprotein-mediated membrane fusion, J. Virol. 73 (1999) 6089-6092. PMCID: PMC112672.

[72] L. Lu, C. Pan, Y. Li, H. Lu, W. He, S. Jiang, A bivalent recombinant protein inactivates HIV-1 by targeting the gp41 prehairpin fusion intermediate induced by CD4 D1D2 domains, Retrovirology 9 (2012) 104. doi:10.1186/1742-4690-9-104.

[73] W. Xu, Q. Wang, F. Yu, L. Lu, S. Jiang, Synergistic effect resulting from combinations of a bifunctional HIV-1 antagonist with antiretroviral drugs, J. Acquir. Immune Defic. Syndr. 67 (2014) 1–6. doi: 10.1097/QAI.0000000000000265.

Figure Captions



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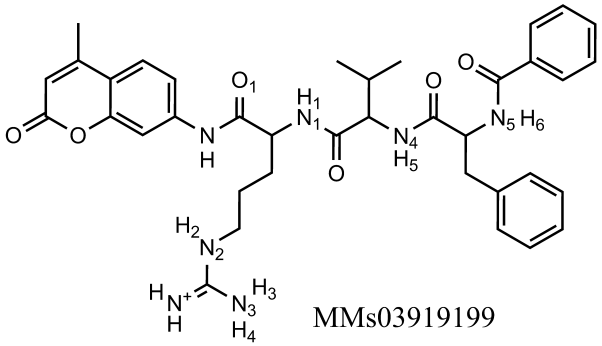

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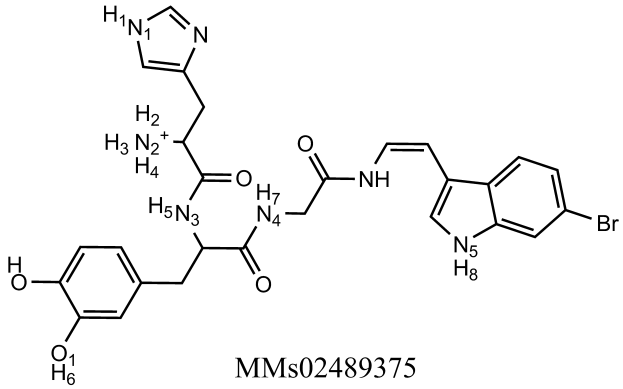

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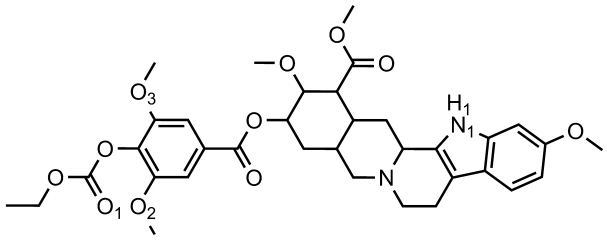

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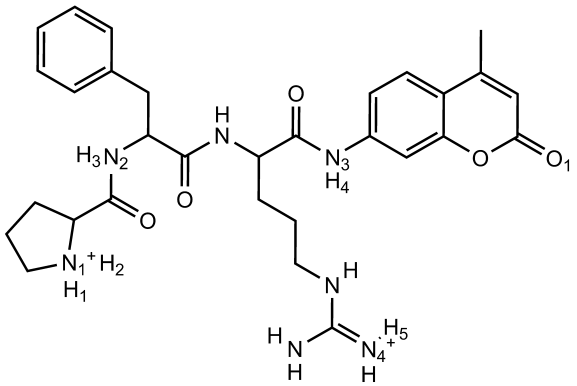

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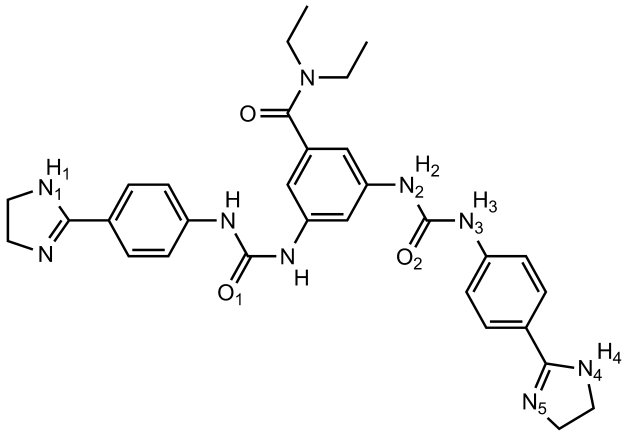

MMs02408883

Fig. 1. Two-dimensional structures of potential peptidomimetics of bNAb VRC01. The molecule codes are from the MMsINC database [49]. Structural elements of peptidomimetics involved in specific interactions with the HIV-1 gp120 protein are indicated (see the text and Table 3).

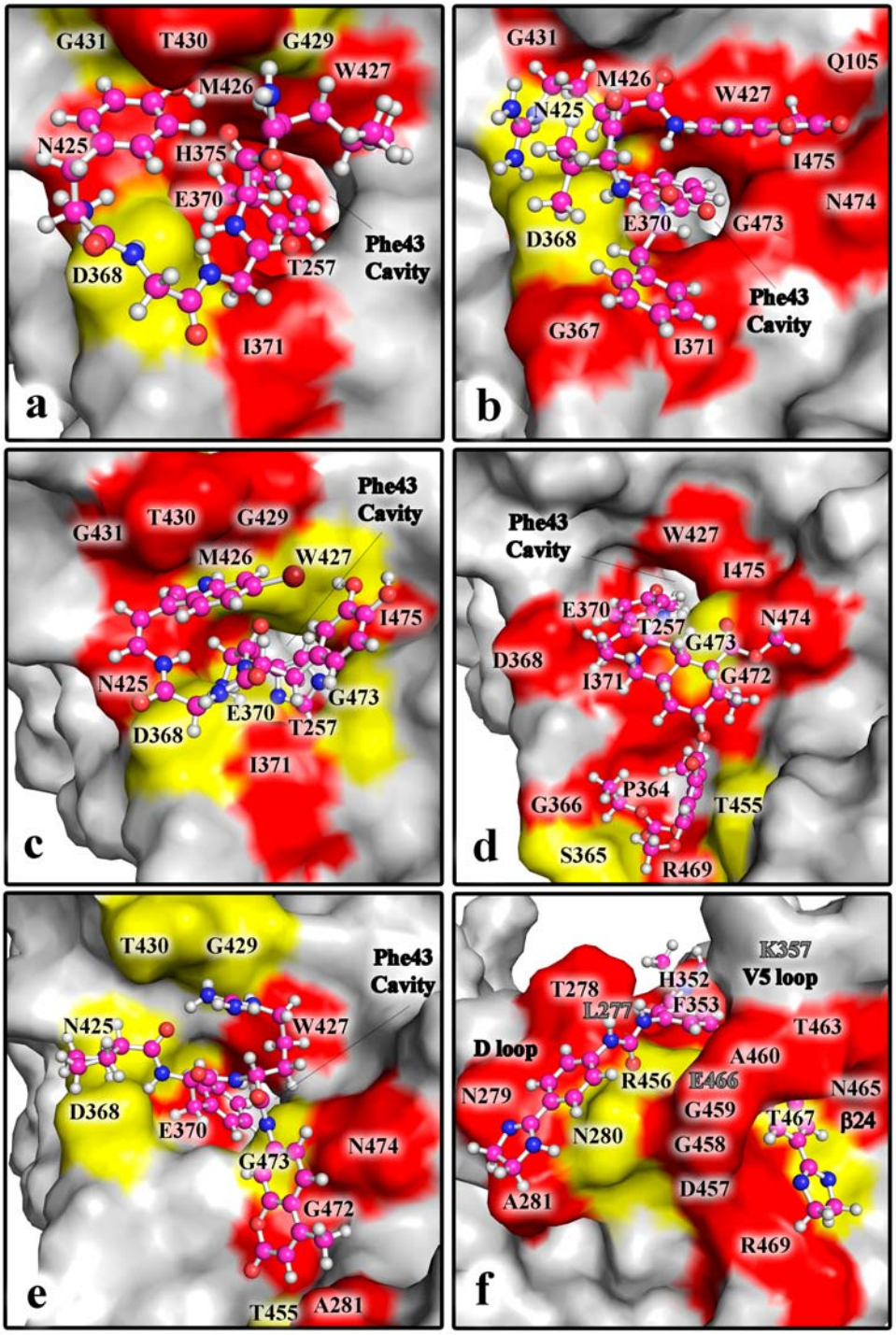

Fig. 2. The docked structures of MMs02391040 (a), MMs03919199 (b), MMs02489375 (c), MMs01727389 (d), MMs03927127 (e) and MMs02408883 (f) with gp120. The Phe-43 cavity of gp120 (images a-e) and its V5/β24/D-loop segment (f) are shown. The residues of gp120 forming hydrogen bonds, salt bridges (Table 3) and van der Waals contacts (Table 4) with the VRC01 peptodomimetic candidates are indicated.

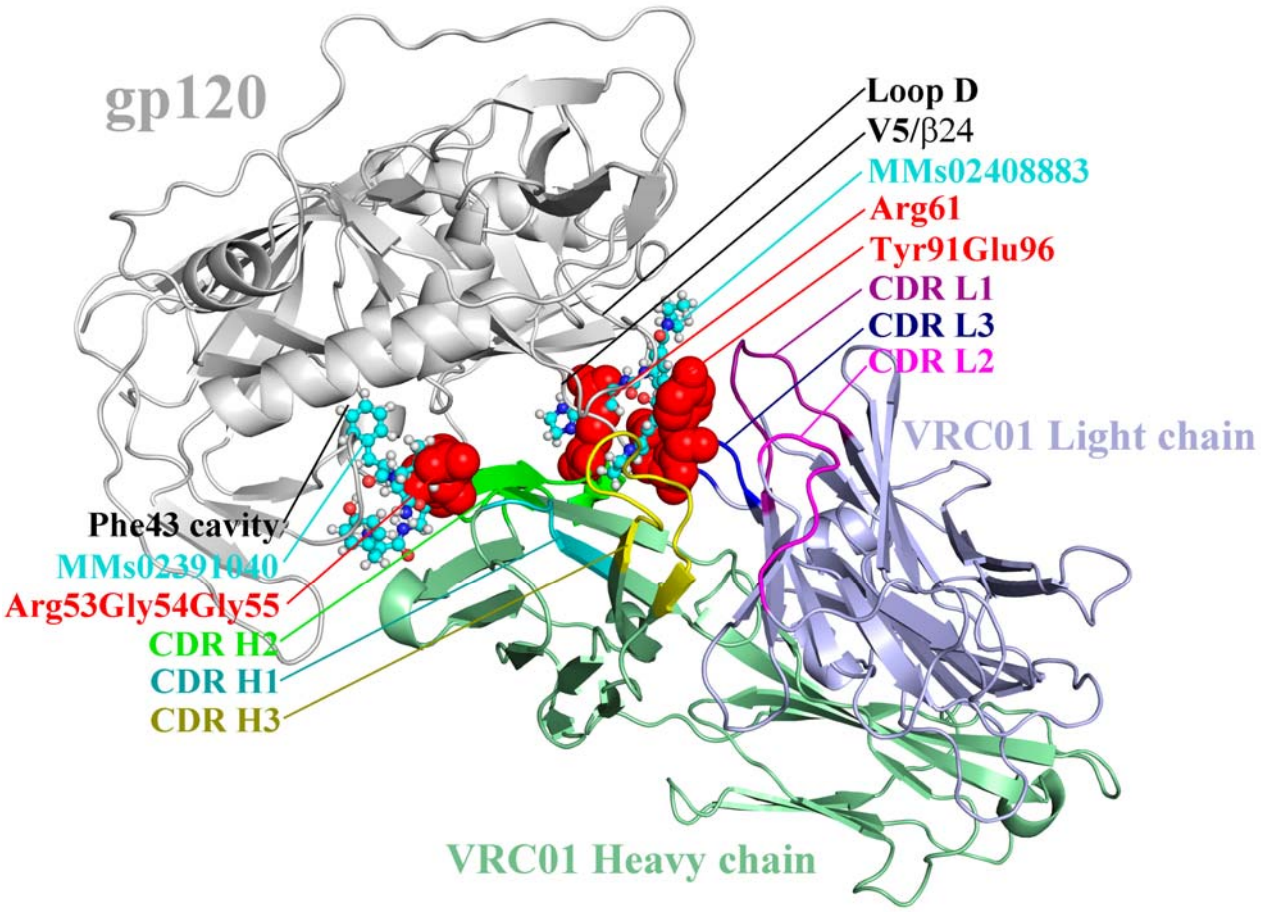

Fig. 3. Superimposed complexes of the HIV-1 gp120 core with the VRC01 Fab and peptidomimetic candidates. The atomic coordinates of the gp120/VRC01 complex were taken from the Protein Data Bank (code 3NGB; http://www.rcsb.org/pdb/) [44]. Structures of the gp120 core and VRC01 Fab are shown by ribbons. Structures of the VRC01 peptidomimetics are shown by a stick-ball-stick model. Only the MMs02391040 compound in complex with gp120 is shown for peptidomimetic candidates masking the Phe-43 cavity of the HIV-1 envelope; the complexes of gp120 with MMs03919199, MMs02489375, MMs01727389 and MMs03927127 coincide with this supramolecular structure. Complementarity-determining regions (CDRs) of the VRC01 heavy and light chains are indicated, as well as the Phe43-cavity and the V5/β24/D-loop segment of gp120. A Corey-Pauling-Koltun (CPK) model is used to highlight the VRC01 residues that are mimicked by the identified compounds.

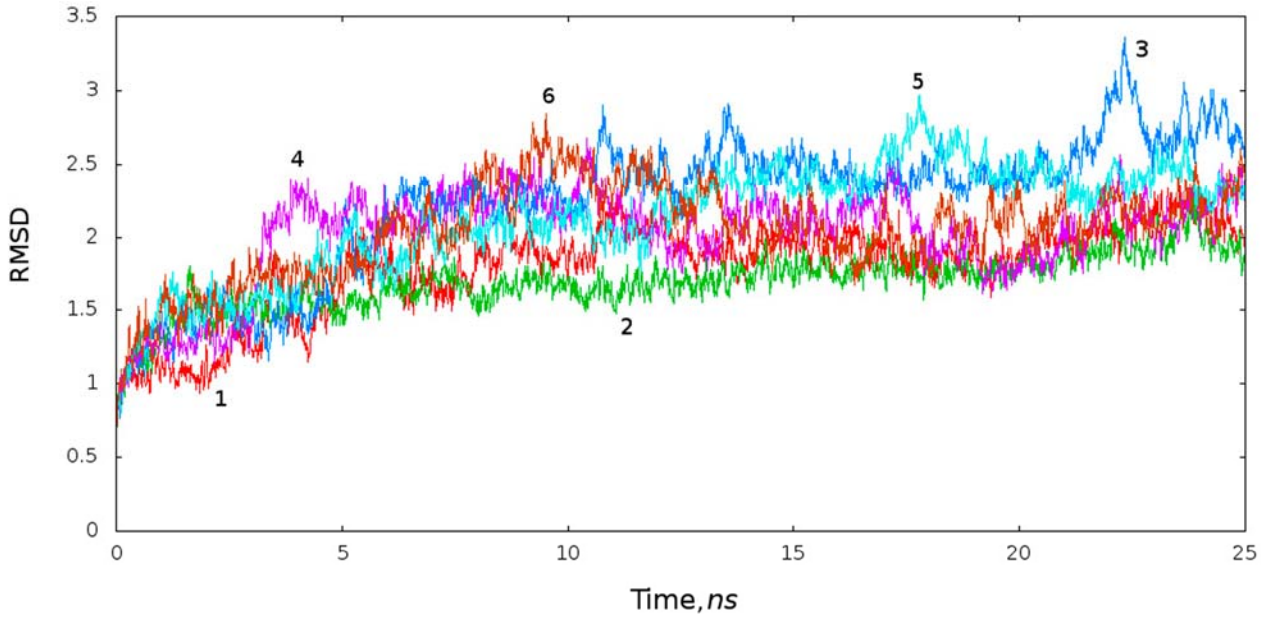

Fig. 4. The time dependence of the RMSD (Å) computed between all of the MD structures and the stating points of the gp120/peptidomimetic complexes. The backbone atoms of gp120 were used in the calculations. The RMSD averages are: MMs02391040/gp120 complex (1) – 1.79±0.32 Å, MMs03919199/gp120 complex (2) – 1.69± 0.20 Å, MMs02489375/gp120 complex (3) – 2.24±0.48 Å, MMs01727389/gp120 complex – 2.01±0.33 Å (4), MMs03927127/gp120 complex – 2.13± 0.38 Å (5), and MMs02408883/gp120 complex (6) – 2.03±0.32 Å.

Tables

Table 1 Input data set used for virtual screening of the bNAb VRC01 peptidomimetics in the MMsINC database.

N	Input data set[a]
1	$Trp50^{H}Lys52^{H}Gly54^{H}Asn58^{H}Tyr59^{H}Arg61^{H}$ $Gln64^{H}Arg71^{H}Asp99^{H}Trp100B^{H}Ser30^{L}Tyr91^{L}Glu96^{L}$
2	$Trp50^{H}Asn58^{H}Arg61^{H}Gln64^{H}Arg71^{H}Glu96^{L}$
3	$Trp47^{H}Trp50^{H}Lys52^{H}$
4	$Asn58^{H}Tyr59^{H}Arg61^{H}$
5	$Arg61^{H}Gln64^{H}Arg71^{H}$
6	$Gln64^{H}Arg71^{H}Tyr74^{H}$
7	$Arg61^{H}Gln64^{H}Arg71^{H}Tyr74^{H}$
8	$Tyr91^{L}Glu96^{L}Phe97^{L}$

Footnote: [a] Superscripts H and L indicate amino acids associated with the VRC01 heavy and light chains respectively.

Table 2 The most promising peptidomimetics of bNAb VRC01.

[a]Compound code	Systematic name	Chemical formula	Molecular mass (Da)	LogP[b]	Number of H-bond donors	Number of H-bond acceptors
MMs02391040	(2R,11S,14R)-11-benzyl-14-carbamoyl-1-(4-hydroxyphenyl)-16-methyl-3,6,9,12-tetraoxo-4,7,10,13-tetraazaheptadecan-2-aminium	$C_{28}H_{39}N_6O_6$+	555.656	-1.48	6	6
MMs03919199	(3R,6R,9R)-14-amino-3-benzyl-6-isopropyl-9-((4-methyl-2-oxo-2H-chromen-7-yl)carbamoyl)-1,4,7-trioxo-1-phenyl-2,5,8,13-tetraazatetradecan-14-iminium	$C_{37}H_{44}N_7O_6$+	682.802	1.06	4	5
MMs02489375	(R)-1-(((R)-1-((2-(((E)-2-(6-bromo-1H-indol-3-yl)vinyl)amino)-2-oxoethyl)amino)-3-(3,4-dihydroxyphenyl)-1-oxopropan-2-yl)amino)-3-(1H-imidazol-4-yl)-1-oxopropan-2-aminium	$C_{27}H_{29}N_7O_5$+	611.477	0.848	8	7
MMs01727389	(1S,2S,3R,4aS,13bS,14aS)-methyl 3-((4-((ethoxycarbonyl)oxy)-3,5-dimethoxybenzoyl)oxy)-2,11-dimethoxy-1,2,3,4,4a,5,7,8,13,13b,14,14a-dodecahydroindolo[2',3':3,4]pyrido[1,2-b]isoquinoline-1-carboxylate	$C_{35}H_{42}N_2O_{11}$	666.724	4.79	1	8

MMs03927127	(S)-2-(((R)-1-(((R)-5-((amino(iminio)methyl)amino)-1-((4-methyl-2-oxo-2H-chromen-7-yl)amino)-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidin-1-ium	$C_{30}H_{39}N_7O_5$+2	577.686	-1.67	3	4
MMs02408883	3,5-bis(3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)ureido)-N,N-diethylbenzamide	$C_{31}H_{35}N_9O_3$	581.681	4.15	6	5

Footnotes: [a] The information is taken from the MMsINC database [49]; [b] The compound lipophilicity.

Table 3 Hydrogen bonds and salt bridges in the complexes of MMs02391040, MMs03919199, MMs02489375, MMs01727389, MMs03927127 and MMs02408883 compounds with the HIV-1 gp120 core.

Compound (ligand)	H-bond [a, b]		Salt bridge [d]
	Static model	Dynamic model [c]	Static model
MMs02391040	N_2H_2...O_{D2}*[D_{368}] N_3H_3...O_{D2}*[D_{368}] N_5H_5...O_{D1}*[D_{368}] O_1...HN[G_{431}] N_1H_1...O[G_{429}]	N_3H_3...O_{D2}*[D_{368}](85.9%) N_2H_2...O_{D2}*[D_{368}](85.0%) O_1H_8...O[M_{426}](64.5%) N_5H_5...O_{D1}*[D_{368}](24.8%) O_1H_8...O[G_{429}](20.3%)	$N_5H_5H_6H_7$ … D_{368}
MMs03919199	N_2H_2...O*[N_{425}] N_3H_3...O_{D1}*[D_{368}] N_4H_5...O_{D2}*[D_{368}] N_5H_6...O_{D2}*[D_{368}]	N_4H_5...O_{D2}*[D_{368}](97.8%) N_5H_6...O_{D2}*[D_{368}](64.4%) N_2H_2...O_{D1}*[D_{368}](24.0%) N_1H_1...O_{D1}*[D_{368}](22.8%)	$N_3H_3H_4$ … D_{368}
MMs02489375	O_1H_6...O[W_{427}] N_2H_2...O_{D2}*[D_{368}] N_1H_1...O[G_{473}] N_2H_3...O*[E_{370}] N_4H_7...O_{D2}*[D_{368}] N_5H_8...O[M_{426}]	N_2H_2...O*[E_{370}](89.8%) N_2H_4...O_{D2}*[D_{368}](62.2%) N_2H_4...O_{D1}*[D_{368}](52.3%) N_4H_7...O_{D2}*[D_{368}](27.8%)	$N_2H_2H_3H_4$ … D_{368} $N_2H_2H_3H_4$ … E_{370}
MMs01727389	N_1H_1 … O[G_{473}] O_1 … HN[S_{365}] O_3 … HO*[T_{455}]	N_1H_1...O[G_{473}](45.1%)	
MMs03927127	N_3H_4...O[G_{473}] O_1…HO*[T_{455}] N_2H_3...O_{D2}*[D_{368}] N_1H_1...O_{D2}*[D_{368}] N_1H_2...O*[N_{425}] N_4H_5...O[G_{429}] N_4H_6...N[T_{430}]	N_1H_1...O_{D2}*[D_{368}](57.5%) N_1H_1...O_{D1}*[D_{368}](52.4%) N_2H_3...O_{D1}*[D_{368}](49.8%) N_1H_2...O*[E_{370}](45.8%) N_2H_3...O_{D2}*[D_{368}](38.0%)	$N_1H_1H_2$ … D_{368}
MMs02408883	N_2H_2...O*[E_{466}] N_4H_4...O*[T_{467}] O_1...HN*[N_{280}] O_1...HN*[R_{456}]	O_1…HN*[R_{456}](60.9%) N_2H_2…O*[E_{466}](52.7%) N_3H_3…O*[E_{466}](50.2%) N_4H_4...O_{D2}*[D_{457}](30.6%) N_3H_3...O*[E_{466}](27.6%) N_2H_2...O*[E_{466}](27.5%) N_5...HO*[T_{467}](21.9%) O_1...NH*[R_{465}](21.0%)	

Footnotes: [a, b] Donors and acceptors of the hydrogen bonds relating to the ligands are shown first, followed by the corresponding functional groups of the gp120 amino acids. Atoms or groups of the gp120 side chains are marked by asterisks. The residues of gp120 are in brackets in one-letter code. Subscripts of oxygen, nitrogen and hydrogen atoms match their numbering in Figure 1. [c] Percentage occupancies of hydrogen bonds are in parentheses. Only hydrogen bonds with occupancies > 20 % are presented. [d] The functional groups of peptidomimetics (Figure 1) and the residues of gp120 forming a salt bridge are indicated.

Table 4 Amino acids of gp120 involved in van der Waals interactions with the VRC01 peptidomimetic candidates.[a]

Peptidomimetic	Amino acids of gp120
MMs02391040	Thr257, Glu370[1], Ile371[1,2], His375, Asn425[1], Met426[1], Trp427[1,2], Thr430[1,2]
MMs03919199	Gln105, Gly367[1,2], Glu370[1], Ile371[1,2], Met426[1], Trp427[1,2], Gly431,Gly473[1,2], Asn474[1,2], Ile475
MMs02489375	Thr257, Ile371[1,2], Asn425[1], Gly429[1,2], Thr430[1,2], Gly431, Ile475
MMs01727389	Thr257, Pro364, Gly366[1,2], Asp368[1,2], Glu370[1], Ile371[1,2], Trp427[1,2], Arg469[1,2], Gly472[1,2], Asn474[1,2], Ile475
MMs03927127	Ala281[1,2], Glu370[1], Trp427[1,2], Gly472[1,2], Asn474[1,2]
MMs02408883	Leu277, Thr278, Asn279[1,2], Ala281[1,2], His352, Phe353, Lys357, Asp457[1,2], Gly458[1,2], Gly459[1,2], Ala460[2], Thr463[2], Asn465[2], Arg469[1,2]

Footnote: [a] Amino acids of gp120 forming the direct contacts with CD4 [65] and VRC01 [44] are marked by superscripts 1 and 2 respectively.

Table 5 Mean values of binding free energy <ΔG> for the complexes of the bNAb VRC01 peptidomimetics with the HIV-1 gp120 core and their standard deviations ΔG_{STD}.[a]

Peptidomimetic	<ΔH> kcal/mol	$(\Delta H)_{STD}$ kcal/mol	<TΔS> kcal/mol	$(T\Delta S)_{STD}$ kcal/mol	<ΔG> kcal/mol	ΔG_{STD} kcal/mol
MMs02391040	-42.7	6.0	-22.8	7.0	-19.9	6.5
MMs03919199	-34.3	7.7	-23.0	8.3	-11.3	8.0
MMs02489375	-31.7	7.0	-23.6	9.0	-8.1	7.9
MMs01727389	-30.4	4.6	-29.2	8.1	-1.2	6.1
MMs03927127	-40.4	9.7	-30.3	6.7	-10.1	8.1
MMs02408883	-33.1	6.1	-24.7	7.3	-8.4	6.7

Footnote: [a]<ΔH> and <TΔS> are the mean values of enthalpic and entropic components of free energy respectively; $(\Delta H)_{STD}$ and $(T\Delta S)_{STD}$ are standard deviations corresponding to these values.