

Computer-Aided Identification of Small-Molecule HIV-1 Entry Inhibitors Mimicking Cellular Receptor CD4

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HIV-1 infection begins with virion entry into target cells through the interaction of viral envelope protein gp120 with its receptor CD4. The binding of gp120 to CD4 induces the exposure of a second binding site for its coreceptor CCR5 or CXCR4. Following binding, the gp41 transmembrane subunit of the envelope protein undergoes a dramatic conformational change to mediate virus-cell membrane fusion, enabling the virus capsid to enter the cell.

Since the HIV-1 entry is initiated by the binding of gp120 to CD4, targeting the gp120–CD4 interface is a cutting-edge approach in the current anti-AIDS drug discovery. Many small molecules that inhibit the interaction between CD4 and HIV-1 gp120 have been developed. However, due to various reasons such as solubility, drug toxicity and drug resistance, these inhibitors have failed to be clinically useful. As such, the identification of novel compounds that block the HIV-1 CD4-binding site is still a research area of considerable interest.

In this study, computer-aided search for novel anti-HIV agents that are able to mimic cellular receptor CD4 was carried out using the pepMMsMIMIC virtual screening platform [1] associated with the MMsINC database [2]. In doing so, the X-ray data on the CD4 amino acid residues responsible for specific interactions with gp120 [3] were used as the input data for pepMMsMIMIC. Potential anti-HIV-1 activity of the CD4 peptidomimetic candidates

found in the MMsINC database was evaluated by molecular docking, molecular dynamics (MD) simulations and binding free energy calculations.

The MD simulations of the twenty top-ranking docked complexes between the CD4 potential peptidomimetics and gp120 revealed five molecules that exposed negative binding free energy values. These molecules were therefore identified as those that may be able to mimic cellular receptor CD4 (Figure 1).

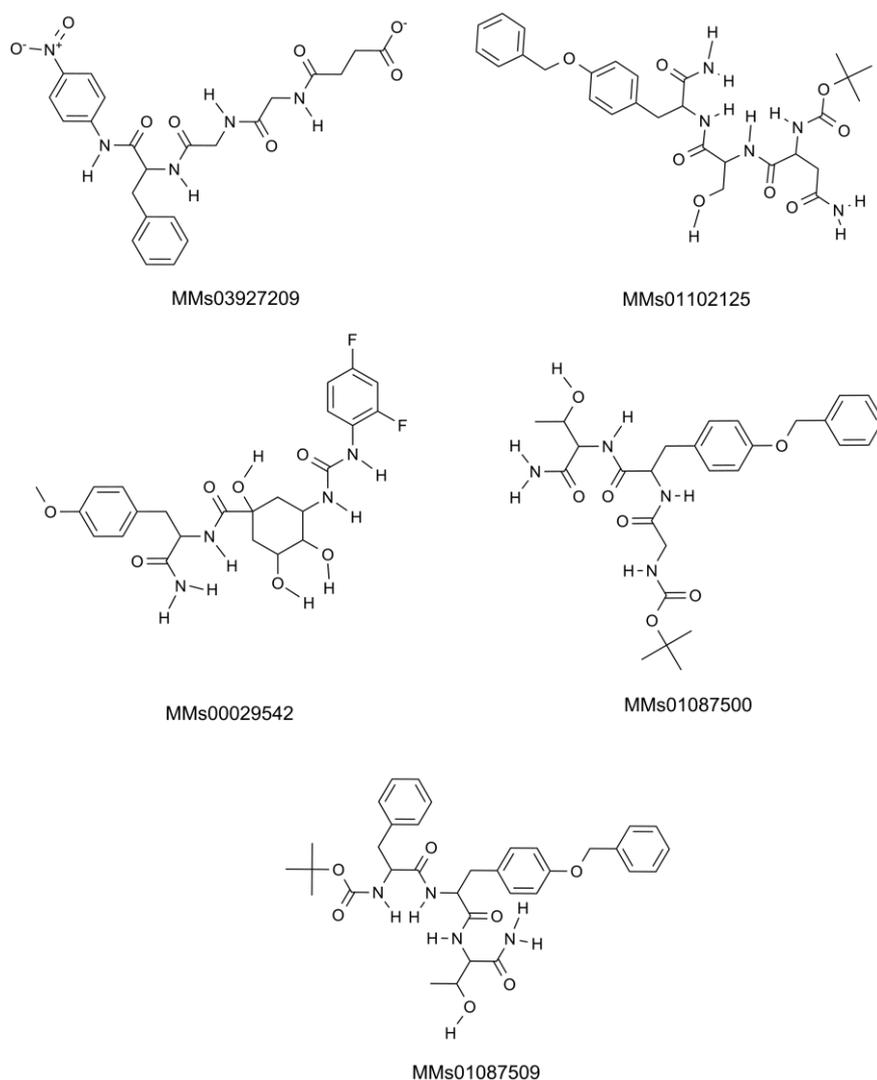


Figure 1. Two-dimensional structures of the CD4 peptidomimetic candidates. The molecule codes are from the MMsINC database [2].

Visualization of the docked structures of the identified compounds with the HIV-1 gp120 core shows that these molecules partially mimic CD4 by specific interactions with the Phe-43 cavity of gp120 playing an important role in the HIV-1 binding to CD4 [3]. In all of the cases of interest, one of the aromatic rings of these compounds is buried into the Phe-43 cavity, resulting in the masking of gp120 residues Glu-370, Ile-371, Asn-425, Met-426, Trp-427 and Gly-473 that are critical at the first step of the HIV-1 entry [3]. For example, aromatic ring of the MMs03927209 compound blocking these gp120 amino acids (Figure 2) actually mimics Phe-43 of CD4, which, obviously, should prevent HIV-1 from the binding to host cell.

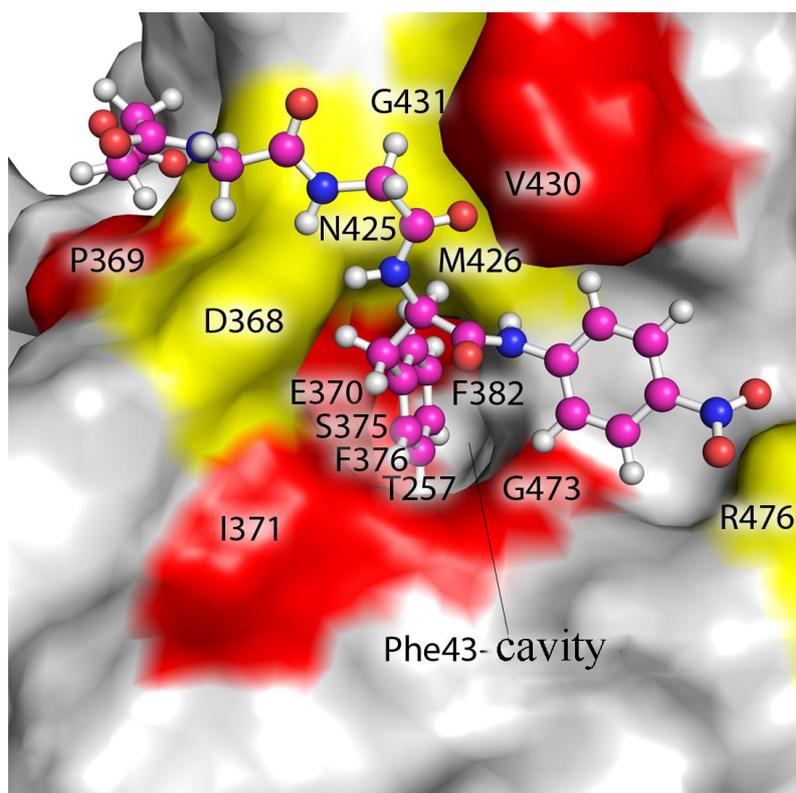


Figure 2. The docked structure of the MMs03927209 compound with gp120. The Phe-43 cavity of gp120 is shown. The residues of gp120 forming intermolecular contacts with MMs03927209 are indicated.

The docked structures of the identified compounds with gp120 exhibit intermolecular hydrogen bonds involving amino acid residues of the HIV-1 envelope that are of great importance to the virus attachment to CD4. All of these compounds participate in the hydrogen bonding with Asp-368 of gp120 that makes critical interaction by forming a salt bridge with Arg-59 of CD4 [3]. The analyzed complexes also expose intermolecular hydrogen bonds associated with such functionally important residues of gp120 as Asn-425 (MMs03927209, MMs01102125, MMs00029542), Met-426 (MMs03927209, MMs01102125, MMs01087500, MMs01087509), Gly-473 (MMs00029542, MMs01087500) and Trp-427 (MMs01102125). The functionally critical residues of gp120 are also involved in van der Waals interactions with the CD4 peptidomimetic candidates. An insight into the MD structures of the complexes of interest indicates that intermolecular hydrogen bonds and van der Waals interactions appearing in the static models dominate the binding. Finally, these complexes are stable within the MD simulations, exposing the low values of free energy of their formation.

Thus, the molecular modeling data suggest that the selected compounds (Figure 1) may be able to neutralize different HIV-1 modifications and, therefore, present potential broad-spectrum HIV-1 entry inhibitors that should be subject to testing for anti-HIV-1 activity against various viral isolates.

References

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