Computer Modeling of Novel Anti-HIV-1 Agents Presenting Water-Soluble Analogs of Glycosphingolipid β-Galactosylceramide

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Novel HIV-1 entry inhibitors targeting the envelope gp120 V3 loop were designed by computer modeling based on glycosphingolipid β-galactosylceramide (β-GalCer) forming on the surface of some susceptible host cells the primary receptor for HIV-1 alternative to CD4, which is used by the virus to enter macrophages and T-lymphocytes (e.g., [1]). To achieve this goal, 3D structures of twelve water-soluble analogs of β-GalCer containing different substitutes of its fatty acid residue were determined by quantum chemical calculations and evaluation of their potential anti-HIV-1 activity was carried out by molecular docking, molecular dynamics and free binding energy simulations. Analysis of the structural complexes of these β-GalCer derivatives with the HIV-1 V3 loops from five diverse viral strains makes it clear that, in all of the cases of interest, the third variable domain of gp120 forms two potential binding sites for glycolipids concerning the immunogenic tip and the base of V3. At the same time, non-conventional XH..π hydrogen bonds between XH sugar groups (X designates C or O) and overlapping π-orbitals of the conserved Phe-20, Tyr-21 and

His-34 residues of the V3 loop were shown to play a key role in specific binding of the designed glycosphingolipids to the above conserved structural motifs of V3 that include residues critical for cell tropism [2, 3]. These findings testifying to the ability of the simulated chemicals to specifically and effectively interact with the functionally important sites of V3 were confirmed by those on molecular dynamics and calculating the free energy of formation of the complexes for these β-GalCer analogs with the HIV-1 V3 loops from different viral modifications. Finally, the majority of the designed molecules were found to form much more stable complexes with V3, compared to the β-GalCer-based anti-HIV-1 agent developed previously [4] and used in the calculations as a control. In the light of the data obtained, these potential HIV-1 entry inhibitors present the promising basic compounds for the development of novel, potent and broad antiviral drugs.

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References

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