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HIV gp120-CD4 inhibitors: Breaking the trend in gp120 structuring with small molecule binding

Judith M. LaLonde[1], Arne Schön[2], Navid Madani[3], Amy M. Princiotto[3], Mark A. Elban[4], Joel R. Courter[4], Akihiro Sugawara[4], Takahiro Soeta[4], David M. Jones[4], Alexander W. Sun[4], Amos B. Smith[4], Joseph Sodroski[3] and Ernesto Freire[2]

[1]Department of Chemistry, Bryn Mawr College, USA
[2]Department of Biology, The Johns Hopkins University, USA
[3]Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, USA
[4]Department of Chemistry, University of Pennsylvania, USA

The low-molecular-weight compound TS-II-224 inhibits infection of HIV-1 by blocking the binding of the viral envelope glycoprotein gp120 to the CD4 receptor and is therefore an important lead as a viral entry inhibitor. Virtual screening and synthesis efforts were used to find substitutes for the Region III tetramethylpiperidine moiety of TS-II-224. These Region III analogs exhibit similar inhibitory activity but bind with diverse thermodynamic signatures. Similar binding affinities can be achieved by different combinations of entropic and enthalpic contributions. However these contributions have functional consequences in the extent of gp120 structuring and the sensitivity to activation of viral infectivity. These compounds demonstrate that gp120 binding affinity, structuring and viral infectivity are dramatically affected by interactions between Region III and the amino acid residues in the vestibule of the gp120 Phe 43 cavity. Analogs that bind within the Phe 43 cavity without driving gp120 structural changes are suitable platforms for further optimization as HIV entry inhibitors.