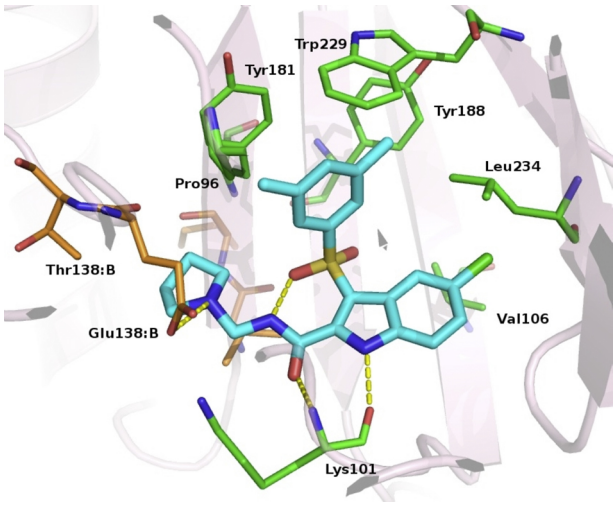

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Anti-HCV Drug Development

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A Novel Family of Multivalent Compounds able to Interact with GP120: Anti-HIV Evaluation and Binding Analysis With Surface Plasmon Resonance

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It is well known that lectins of different origin show interesting properties against HIV replication (Balzarini, 2006). More recent studies support a potential dual mechanism of action for the anti-HIV activity of lectins (Balzarini, 2007; François and Balzarini, in press): (1) directly, by binding to the glycans of the HIV envelope and thus blocking viral entry and (2) indirectly, by favouring deletions in the envelope glycan shield triggering the immune system to recognize previously hidden immunogenic epitopes. However lectins suffer from a number of drawbacks including their high molecular weight, peptidic nature, poor pharmacokinetics, etc. that hamper their development as potential drugs. Based on the key interactions established between lectins and the glycans of gp120, we have designed, synthesized and tested three series of 1,3,5-triazine derivatives (monomers, dimers and trimers) functionalized with aromatic amino acids. These structures are rich in recognition elements meant to mimic the interactions that lectins establish with gp120. The anti-HIV evaluation showed that dimers and mostly trimers exhibit moderate but significant anti-HIV-1 activity in the low micromolar range that is accompanied by the absence of toxicity against CEM cells. Moreover, the most active compounds were subjected to gp120 binding analysis with surface plasmon resonance. The results indicated that some trimers are able to efficiently bind to gp120 with estimated K_D values in the lower micromolar range. Thus, the collected data support the interest of this family of novel anti-HIV agents.

References

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Targeting HCV (+) Strand RNA Genome by a Novel PNA–neamine Conjugate

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The polycationic neamine moiety of the aminoglycoside antibiotic neomycin B was conjugated to a 15 mer peptide nucleic acid (PNA) targeting nucleotide sequence 342–356 downstream of 5′NTR in the core coding region of HCV RNA genome. The cellular uptake of this PNA–nea conjugate is highly efficient and dependent on the concentration of the conjugate in the uptake medium. At as low as 200 nM concentration of fluorescently tagged PNA–nea conjugate, nearly 80% of the cells were fluorescence positive within 6-8 h of incubation. We used MH14 cell culture system carrying stably replicating HCV subgenomic replicons for determining antiviral activity of the PNA–nea conjugate targeting coding start region of HCV core. We noted severe inhibition of HCV replication without any cytotoxic effect on MH 14 cells when anti-HCV PNA–nea conjugate was supplemented in the cell culture medium. We found both HCV replication and translation were efficiently blocked by the conjugate with IC_{50} of inhibition being 200 nM. These results suggest a potential therapeutic application for this class of novel compounds.

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Targeting the Flavivirus Helicase

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Environmental, demographic and ecological reasons suggest that either novel or known flaviviruses will continue to emerge, posing new threats to the human population. Additionally, therapeutic interventions present different outcomes: for example, the success of vaccination against yellow fever virus has been hampered by difficulties encountered when similar programs were launched against dengue virus (DENV). In this context, we are focusing on anti-flavivirus drugs, which should preferably be active against all four DENV serotypes and other flavivirus infections, such as yellow fever virus (YFV), Japanese encephalitis virus (JEV) and tick born encephalitis virus (TBEV). We have therefore extensively studied, among others, helicase (Hel) enzymes involved in the replication process. Starting from crystal structures of these proteins, we identified an unexploited protein site that might be mechanistically involved in Hel catalytic cycle, and which could in principle be exploited for enzyme inhibition. Targeting such new site, we performed *in silico* docking searches using a library of small molecules as a source of potential inhibitors that would bind to the