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Design, Synthesis and Anti-HIV Activity of Some Novel Isatin Derivatives

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Isatin is a versatile lead molecule for designing potential bioactive agents, and its derivatives were reported to possess broad-spectrum antiviral activity. Recently much attention has been devoted to searching for potent antiviral agents for combat HIV/AIDS. We designed and synthesized novel isatine-sulphonamides by microwave technique and characterized them by spectral analysis. We evaluated the broadspectrum antiretroviral activity of isatine-sulphonamide and its derivatives using different strains of HIV-1, HIV-2, SIV and mutant HIV strains. Several isatine-sulphonamide derivatives were found to inhibit HIV-1 (III_B and NL4.3) replication in MT-4 cells We observed no cross-resistance against the fusion inhibitor, nucleoside reverse transcriptase, nonnucleoside reverse transcriptase or protease inhibitor resistant HIV strains. The isatine-sulphonamide compounds were found to inhibit the human immunodeficiency virus type 1 integrase enzymatic activity, HIV-1 integrase binding to target DNA and adsorption of HIV-1 to MT-4 cells, We conclude that it would be interesting to synthesize and evaluate more derivatives of isatine-sulphonamide to identify more selective congeners. These compounds would enable us to determine the structural requirements for inhibition of entry or integration steps in the replication cycle of HIV.

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HIV-1 Resistance to the Anti-HIV Activity of a siRNA Targeting Rev

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HIV-1 replication has a high error rate, making it able to escape from the immune system or from antiretroviral chemotherapies, even from RNA interference (RNAi).

The aim of our study was to evaluate the capacity of HIV to escape from RNAi. For this purpose we generated a SupT1 cell line that stably expresses a small interfering RNA (siRNA) against HIV-1 Rev (SupT1siRNA-Rev) by transducing SupT1 cells with a retroviral vector. This particular siRNA sequence is interesting due to its dual role in HIV-1 Rev and Envelope expression, and because in this region there is only a possible base change that could render a silent mutation both in the Envelope and in the Rev frames.

The replication of the wild-type X4-using NL4-3 in SupT1siRNA-Rev cells is inhibited by a 93%, compared to SupT1 expressing a control siRNA against GFP or non-transduced SupT1 cells. However, we could generate HIV-1 mutants able to overcome the RNAi restriction by passaging virions sequently in SupT1siRNA-Rev cells.

The resistant phenotype was strongly observed only from passage 13, although the subsequent genotyping showed a G/A mutation at position 8513 was starting to appear from passage 11. At passage 14 this first mutation stablished and a C/T change at position 8525 emerged, and stablished in four passages more. The generated mutations are located at the 5′ and 3′ termini of the RNAi sequence, and no changes in the neighbour regions were observed. Both nucleotide mutations are silent in the Envelope frame, but the G8513A produces a Val to Met change in the Rev frame.

The study of this mutation is helpful to better understand HIV evolution mechanisms and their impact into possible future RNAi treatments against HIV.

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Design and Cellular Kinetics of Dansyl-labeled CADA Derivatives with Specific Anti-HIV and CD4 Receptor Down-modulating Properties

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Cyclotriazadisulfonamide (CADA) and derivatives were shown to be inhibitors of HIV replication in human T-cell lines, PHA-stimulated PBMCs and monocytes/macrophages (EC_{50}: 0.3–3.2 μM). The prototype compound, CADA, had consistent activity against laboratory adapted and primary clinical isolates of HIV-1, irrespective of co-receptor preference. CADA acted synergistically when evaluated in combination with various reverse transcriptase, protease and virus entry inhibitors (e.g. T-20). Flow cytometric analysis revealed a significant decrease in the cell surface expression of CD4 in human cells after CADA treatment. Moreover, the anti-HIV activity of CADA correlated with its ability to down-modulate CD4.