high *HLA-C* mRNA levels and higher surface expression of HLA-C protein. Such increase could enhance T cell responses and lead to a better antiviral control over the course of the infection. To study the effect of the 35C/T variant, 249 HIV-infected patients (92 progressors and 157 long-term non-progressors) and 180 HIV uninfected individuals were selected and genotyped for the −35 C/T SNP. In a subgroup of patients, *HLA-C* mRNA levels and responses to peptides containing optimally defined HLA-C restricted CTL epitopes were determined. An overrepresentation of the −35CC genotype was found in the LTNP comparing with the progressor group (p-value = 0.0005). Measurement of *HLA-C* mRNA levels in a subset of individuals, revealed a 1.7-fold increase in subjects with −35CC genotype compared to −35TT genotype, correlating the −35CC genotype with higher gene expression. When assessing responses to HLA-C peptides containing HLA-C restricted epitopes, subjects with −35CC mounted broader responses than those with −35TT or −35TC genotype (median 1.5 in −35CC versus median 0 in −35CT and −35TT). −35CC genotype is associated to slow disease progression putatively due to a higher HLA-C mRNA levels, that at its turn may confer higher reactivity to HLA-C presented HIV-1, possibly leading to a stronger activity of the effector cell. The prior knowledge of the presence of a protective genetic variant influencing HIV disease progression and its functional study could be useful to delay the decision of starting antiretroviral treatment.

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78

Discovery of Novel Natural Neuraminidase Inhibitors (NAI) based on *In Silico* Screening and Antiviral Investigations

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The emergence and worldwide spread of ion channel blocker- and oseltamivir-resistant influenza A viruses ask for the discovery of new highly active antiviral drugs. Recently, we identified and characterized a new potential NAI, katsumadain A, from Alpinia katsumadai by combining computational tools, phytochemical and antiviral approaches (Grienke et al., J. Med. Chem., 2010). Here, the knowledge on compound structure and binding was used for shape-focused virtual screening to identify novel promising compounds with significant enhanced NA inhibitory activity. In the results of virtual screening of the NCI database for biological testing that contains more than 200,000 small organic molecules 5 further natural hit compounds were identified. Three of them are flavonoids – a class of plant metabolites that was repeatedly identified to exhibit interesting antiviral and also NA-inhibiting activity. The NA-inhibiting potential of these compounds was tested with influenza virus A/PR/8/34, 3 clinical H1N1v isolates, and an oseltamivir-resistant H1N1 isolate from the season 2008/09 using a chemiluminescence-based enzyme inhibition assay. All 5 compounds strongly inhibited the NA of the oseltamivir-susceptible H1N1 and H1N1v strains. The best activity exhibited artocarpin, a twofold isoprenylated flavon present in different species of the genus Artocarpus. It was active at nanomolar concentrations. Moreover, its 50% inhibitory concentration was 10-times lower than that of katsumadain A. Artocarpin exhibited also high activity against the NA of the oseltamivir-resistant H1N1 isolate. A potential binding mode of these compounds was determined employing ligand-based techniques and protein-ligand docking using representative protein conformations selected from molecular dynamics (MD) simulations. The insights gained from this modeling study and the SAR data will be exploited for the developing of novel inhibitors of influenza NA with improved resistance profiles.

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79

Synthesis, Anti-HIV and Cytotoxic Activity of Some Novel Isatine-Sulfisomidine Derivatives

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Background: The development of antiviral drugs has provided crucial new means to mitigate or relieve the debilitating effects of many viral pathogens. New classes of inhibitors are essential to combat HIV/AIDS. Isatine is a versatile lead molecule for designing potential antiviral agents and its derivatives were reported to possess wide spectrum antiviral activity.

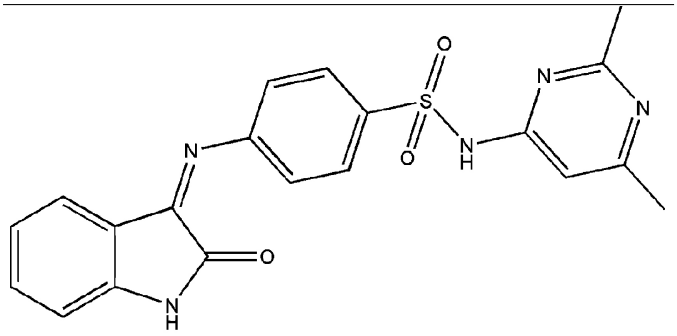
Methods: A series of isatine-sulfisomidine derivatives were screened for antiviral activity against HIV-1 and -2 viruses in MT-4 cell culture. Cytotoxicity of the synthesized compounds was also tested in uninfected MT-4 cells.

Results: All the compounds inhibits the replication of HIV-1 (IIIB) in MT-4 cells (9.22–13.80 μg/ml). The most active compound, SP-A inhibited virus-induced cytopathology by 50% at 9.22 μg/ml and 50% cytotoxicity occurring at a much higher dose more than 125 μg/ml.

Conclusions: SP-A exhibited potency against HIV 1 and are suitable candidate molecules for further investigation.

Anti-HIV activity and cytotoxicity of isatine derivatives.

Compounds	Strain	IC_{50}, μg/ml	CC_{50}, μg/ml
SPIII-A	IIIB	9.22 ± 0.25	>125
	ROD	78.70 ± 5.3	>125
SPIII-B	IIIB	13.5 ± 0	>125
	ROD	>125	>125
SPIII-C	IIIB	12.85 ± 2.33	>125
	ROD	>125	>125
SPIII-D	IIIB	13.80	>89.80
	ROD	>125	>89.80
AZT	IIIB	0.0022	>25
	ROD	0.0011	>25



ISATINE-SULFISOMIDINE

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