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Studies on HIV integrase-LEDGF/p75 interaction inhibitory activity of isatine derivative using the alpha screen luminescent proximity assay

Periyasamy Selvam

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Background

During the early stage of HIV-1 replication, integrase (IN) plays important roles at several steps, including reverse transcription, viral DNA nuclear import, targeting viral DNA to host chromatin and integration. Previous studies have demonstrated that HIV-1 IN interacts with a cellular lens epithelium-derived growth factor (LEDGF/p75) and that this viral/cellular interaction plays an important role for tethering HIV-1 preintegration complexes (PICs) to transcriptionally active units of host chromatin. Small molecule inhibitors of HIV IN/LEDGF have emerged as promising new class of antiviral agents for the treatment of HIV/AIDS. Present work is to study the small molecule inhibitor of HIV IN/LEDGF.

Method

Isatine-sulphadimidine derivative (SPIII-5H) selected for these studies. HIV IN/LEDGF interaction inhibition assay performed by ALPHA screen technique, HIV integrase assay investigated by oligonucleotide based assay and molecular modeling studies also carried by using computational methods.

Results

Lead molecule SPIII-5H inhibits HIV IN/LEDGF interaction (protein-protein interaction) at 10 uM and HIV integrase activity at 6.8 uM. From molecular modeling study indicates that SPIII-5H bind with active site of HIV integrase (DDE), change the conformation and interrupt the binding of HIV integrase with LEDGF.

Conclusion

SPIII-5H novel class of inhibitors of HIV IN/LEDGF interaction and this lead molecule is suitable for further molecular modifications.

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Correspondence: selvaamin@yahoo.co.in
Devaki Amma Memorial College of Pharmacy, Chelembra, Malapuram-673634, Kerala, India