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Design and Synthesis of potent transition state analogs of HIV-1 wild type C-SA protease inhibitors

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Increasing number of HIV/AIDS infected patients and related deaths, along with severe treatment-associated complications, make the HIV/AIDS pandemic more complex than ever.1,2 The introduction of HIV protease inhibitors (PIs) in the mid-1990s dramatically changed the situation for HIV/AIDS patients.3-6 Combination therapy initially including one protease inhibitor and two nucleoside reverse transcriptase inhibitors, the so-called highly active antiretroviral therapy (HAART) furnished a sharp decline in HIV/AIDS related mortality for patients receiving this therapy.[7,8]

Based on this concept we have designed and synthesized eleven novel PCU-lactam peptide analogs with the modification of substituent amino acids. It was shown that the lactam bond of compound 5 is virtually non-hydrolyzable.

The rationale behind using the cage lactam is that when it is incorporated into a short peptide, this cyclic amide bond could perhaps serve as non-cleavable peptide bond under protease conditions. The lactam hydroxy group could also serve as a transition state mimic since it is a norstatin type isoster

(Fig 1). If that were to be the case, then this family of cage peptides could potentially exhibit HIV protease inhibitor characteristics.

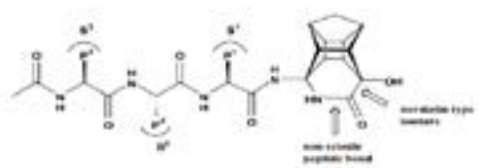

Figure 1: General structure of proposed non cleavable pentacylcloundecane-lactam Norstatin type HIV-1 protease inhibitor.

In conclusion, all eleven synthesized novel compounds displayed good inhibitory activity against wild type C-SA HIV-1 protease in which compound 6a and 6k being the most potent compared to reference standards atazanavir and lopinavir. These novel compounds are expected to have an improved membrane permeability imposed by the PCU skeleton. Their activity is expected to remain analogous under in vivo testing since the PCU should have the added advantage of increased permeability across the cell membrane. Further optimization as well as in-depth structural and biological studies of the selected protease inhibitors are the subject of our ongoing investigation

Speaker Biography

S.N. Sriharsha completed his doctorate in Medicinal Chemistry. He is a Principal, Professor, and Research Director, Hill Side College of Pharmacy and Research Centre and Academic Council Member RGUHS. Industry worked at Senior Positions: Dr. Reddys Bangalore, Biocon and Mili Health care (Russian Based Company), New Delhi. Awards and Achievements:Key note Speaker in International drug Discovery conference on Pharmaceutical Science and drug manufacturing in Thailand 2021. Presented Research paper against corona virus. Key note Speaker in International drug Discovery conference on Pharmaceutical R&D and Biopharmaceutics in Kaulalumpur, Malaysia 2019. Presented HIV drug discovery paper. International Advisory board in Bioleagues. Award for the Excellency in Scientific Research in 2018 in recognition to significant contribution in the field of Research and Development in Oriental University, Indore, MP. Director Pharma Companies:Bhuvika Health Care Bangalore and Mili health care, New Delhi. Services: Pharma Technical consultancy services R&D(Synthetic and formulation), Plant set up, Exports, contract manufacturing, regulatory, BA/BE studies, Clinical, analytical support, DMF and Dossier support etc.

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