Synthesis of novel CCR5 antagonists for HIV-1 infection

The project aims to develop a CCR5 antagonist drug for the treatment of HIV-1 infection. HIV-1 virus uses a co-receptor, CCR5, for viral entry and subsequent infection of host cells. This is an essential step, especially in early infection. One CCR5 antagonist has received FDA approval despite concerns over potentially fatal liver toxicity. Also, known drug resistance to existing products, creates an urgent need for the development of novel drugs, especially in newer classes, that would make treatment effective.

We propose to firstly synthesize drugs that will overcome this problem and additionally, in extended work, to target therapy to cells and areas of the body that are most susceptible to virus infection and residence via liposome-mediated delivery.

Based on a literature review on synthesis and activity of CCR5 antagonists, and their development as HIV-1 drugs, we have identified a novel series of readily accessible compounds that do not appear in patent literature, although related templates have been reported to have antibacterial activity (WO2005/026149; EP1426366). Drug synthesis has literature precedent, appears straightforward starting from commercially available raw material precursors. An advantage is that the stereochemistry present within the drug targets, which may play a role in determining/enhancing the biological activity.

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