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Design and development of new anti-HIV agents based on quinolone scaffolds

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HIV infection is a major challenge to humanity, and a definitive cure or a viable vaccine for HIV is still elusive. HIV-1 is constantly evolving and developing resistance against clinically used anti-HIV drugs. Thus, it leads to serious hurdles in the treatment of HIV infection. This prompts the need to develop new anti-HIV drugs; preferentially adopting intelligent ways to counteract an evolving virus.

Multi-targeting ligand is a modern strategy by which various druggable targets can be exploited using a single chemical entity. Such a prospective drug, when acting on multiple sites is much more effective than the one acting on a single target. This could not only counter the problem of developing drug resistance but also help in improving patient compliance with simpler regimes. Reverse transcriptase (RT) and Integrase (IN) are two pivotal enzymes in the HIV-1 lifecycle having high structural/functional analogy and overlapping pharmacophoric requirements, to be perceived as targets for novel dual-purpose inhibitors. Using already reported quinolone-based RT and IN dual inhibitors, we performed ligand-based virtual screening to find potential leads, which were further screened through molecular docking with the selected target proteins. This helped us to identify potential quinolone-based scaffolds with the potential to inhibit both enzymes HIV-1 RT and IN.

By fusing the 4-quinolone core with a carboxamide at C-3 and attaching aliphatic and aromatic substituents at N-1 and C-6, we synthesized a total of 160 novel compounds in 4 distinct chemical series (Series A, B, C, and D). A modified and highly efficient synthesis methodology was employed. Among the synthesized compounds, fifty compounds were tested for their anti-HIV potential in cell-based anti-HIV assay.

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Biography

Nafees Ahemad is Senior Lecturer at Monash University Malaysia (MUM). He obtained an M.S. (Pharm) and Ph.D. in Natural Products Chemistry/Medicinal Chemistry from the National Institute of Pharmaceutical Education and Research (NIPER), Mohali, India. He was also a Postdoctoral Research Fellow in the Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM) Penang. He has been working in academia for more than 15 years. He worked on the total synthesis of natural products, and the synthesis of new chemical analogs for the discovery of new anti-HIV agents based on natural product templates. His current areas are computational-based rational design and synthesis of new drug candidates for HIV-1, dengue, and other therapeutics. His interest also includes natural products isolation and total synthesis of natural products. He has published more than 60 research papers, and many book chapters and presented his work at various conferences.

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