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Novel Lipid-Functionalised PNA Monomers as Potential HIV-1 Non-Nucleoside Reverse Transcriptase and/or Integrase Inhibitors

Despite the considerable success in Western countries of highly active anti-retroviral therapy (HAART), AIDS still remains one of the most urgent world health problems, being the first cause of death in Africa and the fourth leading cause of death worldwide. HAART typically involves a cocktail of three drugs given in combination, which act on two different biological targets in the HIV-1 life cycle e.g. two nucleoside inhibitors of HIV-1 reverse transcriptase (NRTIs) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Unfortunately, the efficacy of this current therapy is often hampered by the rapid emergence of drug resistant HIV-1 variants, the severe side-effects associated with both short- and long-term treatments and medication costs. These findings, when taken together with the fact that existing drugs do not completely eradicate the virus from the body and so must be taken chronically, highlight the continuing need for new anti-HIV drugs which are less toxic, active against the common drug resistant mutants selected by present treatments and/or inhibit novel biological targets in the viral replicative life cycle.

In an attempt to address some of these issues, we have recently embarked upon the development of novel NNRTIs and HIV-1 integrase (IN) inhibitors. HIV-1 IN, the enzyme responsible for the integration of proviral DNA into the host genome, has emerged as an attractive target for future anti-viral therapies because it has been found to play a key role in stable infection and there appears to be no functional, human equivalent. As part of this research, we have prepared and evaluated a range of *N*-terminal lipid-functionalised peptide nucleic acid (PNA) monomers as potential inhibitors of RT and/or IN. From these studies, one compound has been identified as worthy of further development due to its unusual structure and interesting activity profile; it is endowed with both anti-HIV-1 RT and IN activity. *All the compounds examined in this study were structurally analysed by the EPSRC National Mass Spectrometry Service Centre.* This work has recently been published.¹

1. Thomas, M.G.; Maga, G.; Mouscadet, J.-F.; Howarth, N.M. *Nucleosides, Nucleotides & Nucleic Acids* **2007**, 26, 1063-1066