The identification and synthesis of allosteric integrase inhibitors.

David Olowookere, Dr Mark Ashton
Email: d.i.olowookere2@Newcastle.ac.uk

Newcastle University, School of Pharmacy.

Background

In 2016 it was recorded that 36.7 million people were living with HIV and 20.9 million people are on antiretroviral therapy. The Human immunodeficiency virus-1, it is one of the retroviruses from a diverse family of RNA viruses that synthesize a DNA copy of their RNA genome after infecting the host cell[1].
A large nucleoprotein complex derived from the retrovirus is introduced into the cytoplasm of the host cell, this complex is essential in the integration of the viral DNA. This process is mediated by the viral integrase enzyme (IN) and is an essential step in viral replication. IN and Lens Epithelium-Derived Growth Factor (LEDGF)/p75 act as a bimodal tether during integration of the HIV-1 at the site of active genes and integration is dependent on their interaction and affinity to bind along the bodies of active genes[2].
Although there are treatments for HIV targeting the three viral enzymes, including IN, there are issues with drug safety and viral resistance . New drugs are therefore needed to improve the safety profile and overcome resistance. Targeting IN via an allosteric mechanism and hence blocking its interaction with LEDGF/p75 offers two advantages; inhibition of the integration of viral DNA and prevention of maturation (production of infectious viral particles)[3,4] . HIV-1 IN has been identified to have 3 domains the N-terminal, catalytic core domain (CCD) and the C- terminal domain. A tetramer of IN (requiring the interaction with LEDGF/p75) catalyses the insertion of viral DNA into the host cell's DNA[2].
This project looked to develop novel small molecules capable of inhibiting the IN-LEDGF/p75 interaction.

Methods

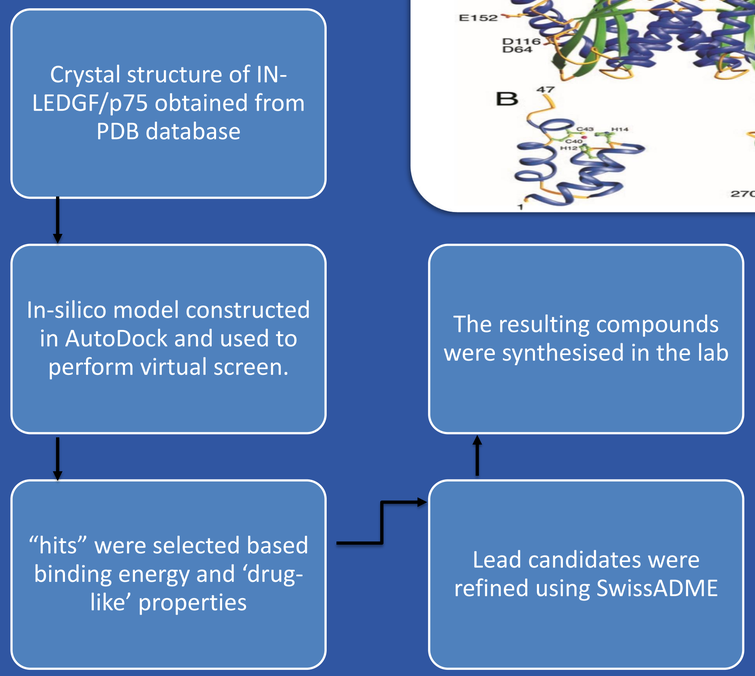

Figure 1: overview of the *in- silico* screening

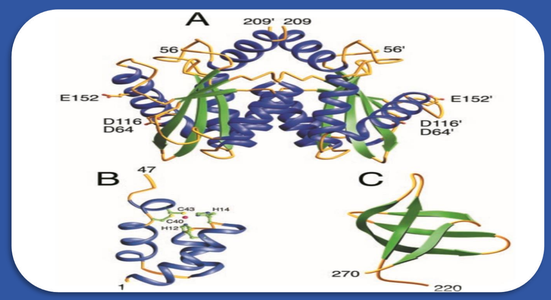

Figure 3. Structure of the 3 domains HIV-1 integrase. A, the catalytic core domain; B, the N-terminal domain; C, the C-terminal domain. Protein Data Bank codes are 1BIS, 1WJC, and 1IHV, respectively[2].

Result

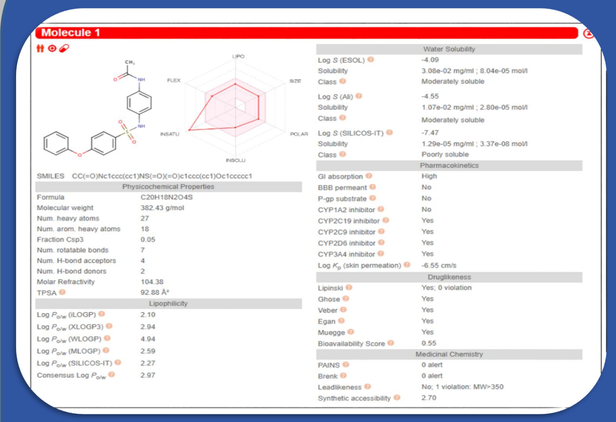

Figure 3. Pharmacokinetics properties of N-[4-(4-phenoxybenzenesulfonamido)phenyl]acetamide[5].

Following filtering with SwissADME, the best compound both in terms of favourable 'drug-like' characteristics and ease of synthesis was selected for preparation.
Although some progress was made towards the synthesis of the target, a number of issues were encountered which resulted in the failure to obtain the lead.

Further work

Complete the synthesis of the lead and undertake the biological testing.

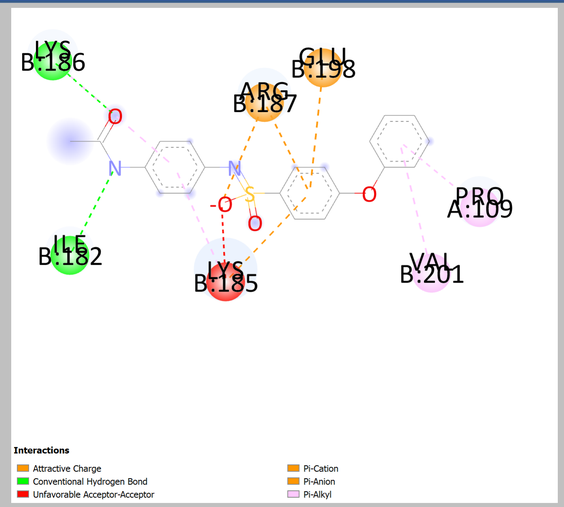

Figure 3. Structure showing the different binding interactions of N-[4-(4-phenoxybenzenesulfonamido)phenyl]acetamide.

References

1.Unaids.org. 2018 [cited 25 September 2018]. Available from: http://www.unaids.org/en
2. Engelman A, Kessl J, Kvaratskhelia M. Allosteric inhibition of HIV-1 integrase activity. Current Opinion in Chemical Biology. 2013;17(3):339-345.
3. Craigie R. HIV Integrase, a Brief Overview from Chemistry to Therapeutics. Journal of Biological Chemistry. 2001;276(26):23213-23216.
4.Cherepanov P, Ambrosio A, Rahman S, Ellenberger T, Engelman A. Structural basis for the recognition between HIV-1 integrase and transcriptional coactivator p75. Proceedings of the National Academy of Sciences. 2005;102(48):17308-17313.
5. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017;7(1).

'This research made use of the Rocket High Performance Computing service at Newcastle University'