The identification and synthesis of novel allosteric integrase inhibitors targeting HIV-1

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Aims

- Using data collected from the protein data bank, to run screening through AutoDock to determine potential lead compounds
- To perform a small scale in-silico study on some of the current leads identified to assess key physiochemical parameters and possible similar structures (Swiss Similarity; swisssimilarity.ch)
- To synthesise one of the leads compounds identified for biological testing and characterise the novel compound

Introduction

AIDS results from the systemic replication of the pathogenic lentivirus human immunodeficiency virus type 1 (HIV-1), which in the majority of cases, if unchecked will destroy the host immune system. [2]

The project focuses on targeting a specific viral enzyme; HIV-1 integrase (IN), which is an important therapeutic target in the fight against HIV/AIDS. The enzyme enables HIV to insert its own genetic material into the DNA of a human host cell. The integrase tetramer, bound to viral DNA, interacts with host LEDGF/p75 protein to allow integration to active genes. [2]

Despite success, antiretroviral therapy still presents challenges. Significant numbers of new infections are mediated by drug-resistant viral strains. Furthermore, there is a need for therapeutic agents with better safety profiles, since most patients are expected to be taking the drugs long-term. Development of novel compounds that inhibit previously unexploited aspects of the viral lifecycle, is currently one the best lines of attack against HIV/AIDS. [2]

In the past, drugs have been developed which work by affecting integrase at its active site. A newer approach involves allosteric inhibition, targeting the enzyme at another region other than its active site. The result of allosteric inhibition is that the virus is no longer able to produce new viral particles.

Epidemiology

There are currently 36.9 million people living with HIV (2017). However, the number of AIDS-related deaths worldwide has been reduced by more than 51% since the peak in 2004. Significant progress made over the past 15 years, mainly credited to the use of highly active antiretroviral therapy (HAART), which in turn has inspired a global commitment to end the epidemic by 2030. [1]

Project Overview

The project involved 2 different stages:

1) Lead identification (*in-silico*)
2) Synthesis of a lead compound, shown as (III) in *Figure 1*.

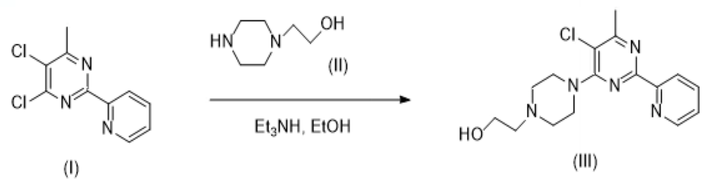
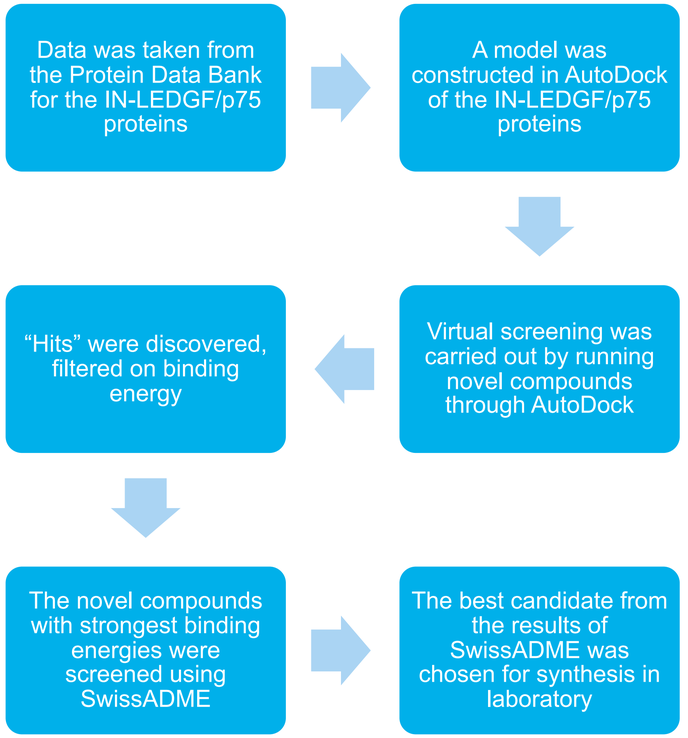


Figure 1- A reaction scheme showing the synthetic route adopted.

Methods



Results

- The results of screening the novel compounds and binding energies through AutoDock produced "hits", from which the highest binding energy with the lead compound is shown in *Figure 2*.
- The results of running the Swiss ADME programme showed the compound identified to have good predicted chemical properties for a potential drug, shown in *Figure 3*.
- The properties included: High GI absorption, moderate solubility, a logP of 3.04 and bioavailability of 0.55.

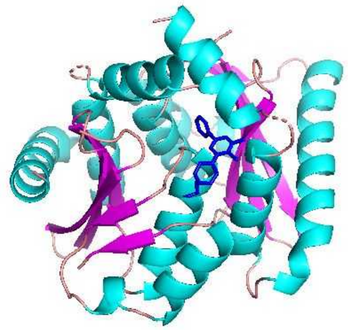


Figure 2- The lead compound bound to LEDGF/p75 in position of highest binding energy

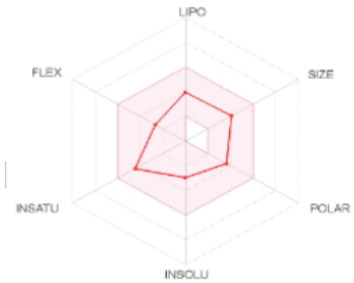


Figure 3- Bioavailability Radar of lead compound produced by SwissADME

After carrying out the synthetic route shown in Figure 1, the results were unclear as to whether the lead compound had been successfully synthesized. This was due to time constraints and a small supply of starting materials to work with, which lead to the testing of the final product via IR and ^{1}H NMR spectroscopy producing unclear and varied data.

Conclusions

- The binding energies simulated from screening the novel compounds in AutoDock show that the compounds identified have potential activity
- Screening with SwissADME showed that the lead identified doesn't have all ideal physiochemical characteristics but could have potential for development as a drug
- Future work would include completion of the synthesis of the lead; completion of an *in-silico* Structure Activity relationship study (SAR) and biological screening.

Acknowledgements

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References: [1] Global HIV & AIDS statistics — 2018 fact sheet http://www.unaids.org/en/resources/fact-sheet
[2] Allosteric inhibition of HIV-1 integrase activity, Engelman A, Kessi J. J, et al. Current Opinion in Chemical Biology. 2013 June ; 17(3): 339–345