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

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ABSTRACT

This research was carried out to enhance the lives of those with HIV/AIDS. The study involved developing a drug that can enter the body and prevent the action of a specific viral enzyme. Inhibition of the enzyme will results in the virus being unable to replicate. Although medications in the past have been developed that can stop viral replication this drug will be unique since the bespoke mode of action will prevent any virus in the body developing resistance to the medication.

INTRODUCTION

The human immunodeficiency virus (HIV) is an epidemic that affects millions of people globally. It was predicted that in 2016 around 36.7 million people were living with HIV worldwide [1]. Of the 36.7 million people infected 1 million died in 2016/2017. The ultimate goal is to eradicate this epidemic by 2030[1].

Current medications used in the treatment of HIV can prove to be unsuccessful due to two main reasons. Firstly the safety profiles of the medication, especially as this medication will be taken for the rest of the patients life. Secondly HIV can develop resistance to medication very easily [2]. It is found that even in patients that have good adherence to the medication and take it as prescribed, resistance can occur. With this in mind it was clear a medication must be produced that HIV cannot become resistant too. The objective was to develop compounds that stop the viral enzyme integrase (IN) from binding to the host cell protein, Lens Epithelium Derived Growth Factor p75 (LEDGF/p75).

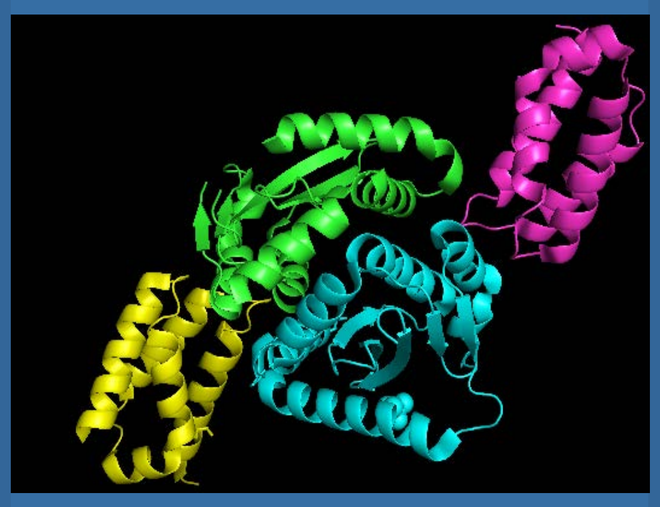

Figure 1: LEDGF/p75 and integrase complex

The interaction between IN and LEDGF/p75 is important for two reasons; the interaction between IN-LEDGF/p75 allows the formation of IN tetramers which are critical for correct enzyme function, and LEDGF/p75 allows IN to tether to the host cell DNA, and hence integrate the viral DNA into the host DNA.

RESULTS

ADME data showing the absorption, distribution, metabolism and excretion of the compounds. This pharmacokinetic data is very useful when designing a drug, allowing compounds to be discarded if they showed unfavorable aspects. An advantage of this compound is that it crosses the blood brain barrier (BBB) which the majority of HIV treatment cannot do.

Figure 4 shows the binding location of the lead compound against its target, with specific binding interactions indicated in Figure 5. The data clearly indicates that the binding interaction is largely hydrophobic in nature.

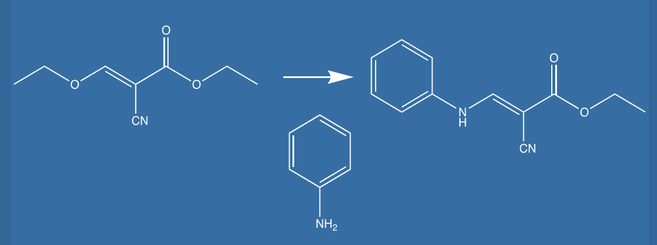

Figure 2: synthetic route employed to synthesize the lead compound.

METHODS

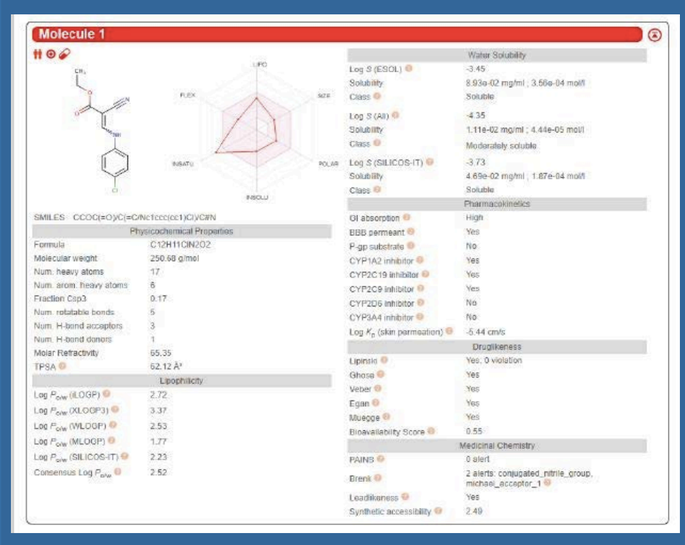

Figure 3: Results of SwissADME simulation

The integrase-LEDGF/p75 (data taken from the Protein Data Bank) complex data was used to construct an *in-silico* model using AutoDock. The University's High Performance Computing facility, Rocket was used to run a virtual screen against a database known as Zinc15, a database with hundreds of millions of compounds. Lead compounds were selected based on their binding affinity to IN-LEDG/p75. The lead compounds were further screened using SwissADME (Figure 3), the knowledge gained from this program allowed for refinement of the leads to make compounds that inhibits HIV but can also be synthesized, and have favorable physiochemical properties.

The compound were synthesized in the Medicinal Chemistry labs in the School of Pharmacy in accordance to a literature protocol [3].

CONCLUSIONS AND FUTURE WORK

Over the six weeks a vast amount of screening and modeling took place in order to ensure the best compound was selected. Once the compounds were selected synthesis began. By the end of the six weeks two compounds were successfully produced and ready for further testing.

Future work would involve the biological assessment of the lead compound, and additional modelling to explore a Structure Activity Relationship of a series of analogues. Careful consideration would also need to be given to the metabolic stability of the ester component of the lead and alternative bioisoteres considered.

ACKNOWLEDGEMENTS

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Figure 4: A model of the synthesized compound interactions with integrase, preventing the LEDGF integrase complex being formed

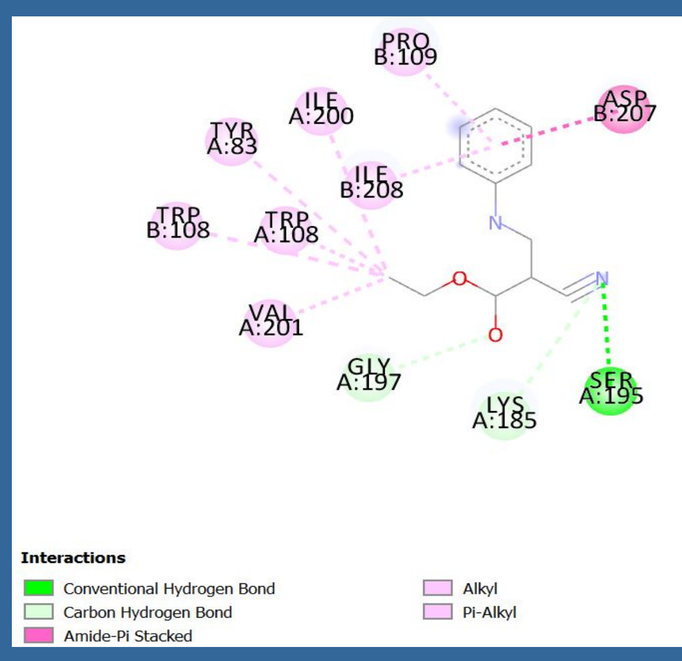

Figure 5: Binding interaction between synthesized compound and protein.

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