The Identification and synthesis of novel allosteric inhibitors

Posters

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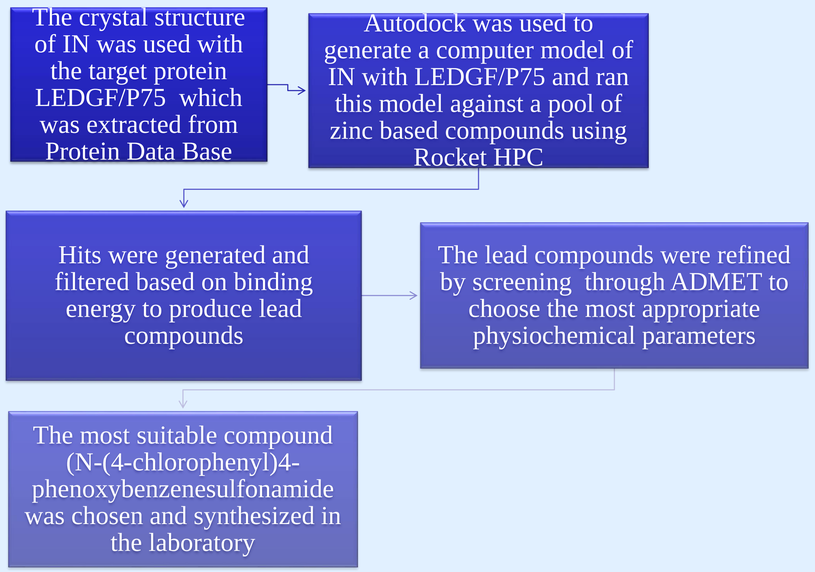
Introduction

HIV (human immunodeficiency virus) is a lentivirus which can lead to acquired immunodeficiency virus (AIDS). In the last 25 years the number of new infections has reduced from 3.5 million to 2.1 million[1]. The magnitude of this improvement is partly a consequence of the highly active antiretroviral therapy (HAART), which targets the activities of the viral reverse transcriptase, integrase and protease enzymes that are critical for the viral replication[2]. However there is a need for new treatments as drug resistant strains are becoming more common[2]. Retroviral integrase (IN) is an enzyme responsible for the insertion of the viral DNA into the host chromosomal DNA, an essential step for HIV replication[2,3]. Inhibitors currently exist which target the active site of the viral-encoded integrase in the early phase [3]. This project however focuses on the new approach which targets the interaction between integrase and the cellular host factor LEDGF/p75.

Methods



Overview of in silico screening

Results

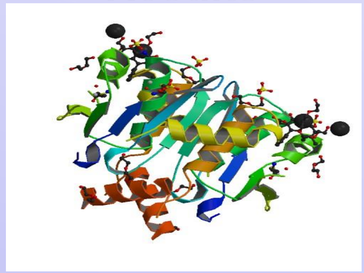


Figure 1. Interaction between LEDGF/p75 and IN[4]

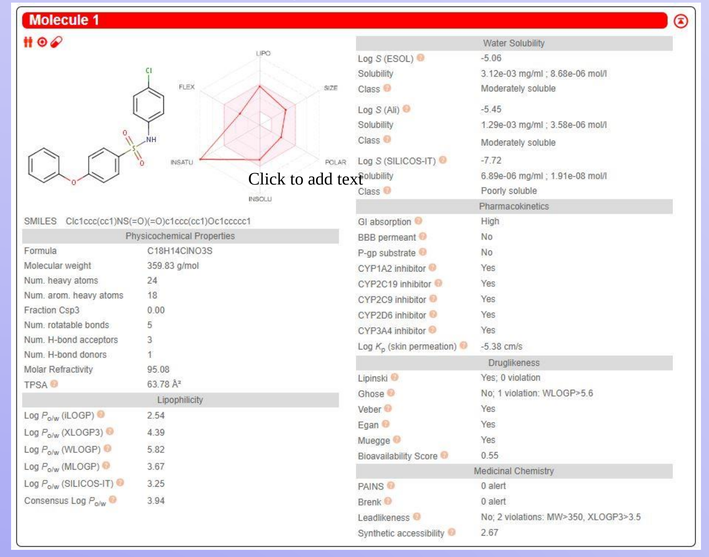


Figure 2. Predicted properties of the chosen drug[5]

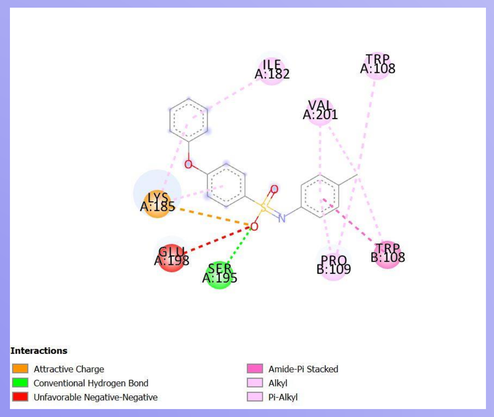


Figure 3. Binding properties of the drug

Discussion

The chosen compound was found to be a suitable inhibitor using ADMET (figure 2, 3), however the compound inhibits CYP3A4 which is a key enzyme involved in the metabolism of various drugs (figure 2). Therefore it could lead to drug-drug interactions in patients. The compound is also predicted to have a good GI absorption hence would be a suitable candidate for oral administration. In addition, the compound is predicted not to penetrate the blood brain barrier therefore eliminating the associated side effects.

Conclusion

- The chosen compound has proven to be an effective inhibitor of LEDGF/P75 and could potentially be developed. Due to a time constraint , we were unable to complete the synthesis and in vivo testing of the proposed compound. The drug will also need to be tested with live tissue to ensure efficacy and safety before it can be further developed.

References

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Acknowledgements

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