The identification and synthesis of novel allosteric integrase inhibitors

Newcastle University
z.m.latt2@newcastle.ac.uk

Zena Latt*, Mark Ashton **School of Pharmacy**

Introduction

- Human immunodeficiency virus (HIV) is a type of retrovirus that is transmitted through contaminated body fluids, including blood and semen[1].
- Infection with HIV can lead to acquired immunodeficiency syndrome (AIDS).
- Recently, drugs have been developed to reduce the risk of infection after transmission of HIV-1.
- Current drug regimens include the use of reverse transcriptase inhibitors, integrase inhibitors and protease inhibitors[2].

HIV-1 integrase (IN) is an enzyme that allows the insertion of viral DNA into the DNA of the host. HIV-1 IN targets the $CD4^+$ T cell of the host, using the Lens Epithelium Derived Growth Factor p75 (LEDGF/p75) protein to tether the enzyme to the chromatin[3]. The overall effect of the HIV-1 virus is to reduce the CD4 cell count. Low concentrations of T cells cause damage to the immune system, thus making the host more susceptible to further infection. The mechanism behind integrase inhibitors is to prevent viral replication. Currently, the marketed integrase inhibitors target the active site of the enzyme. Novel integrase inhibitors are presently being developed to prevent IN-LEDGF/p75 binding via an allosteric mechanism thereby blocking viral replication[4].

Aims

- Use AutoDock and SwissADME to prepare and select the top compounds.
- Synthesise the best allosteric integrase inhibitor candidate.

References

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3. Poeleschla, EM. (2008) 'Integrase, LEDGF/p75 and HIV replication', *Cell Mol Life Sci.*, 65(9), pp. 1403-24.
4. Engelman, A, et al. (2013) 'Allosteric inhibition of HIV-1 integrase activity.', *Curr Opin Chem Biol.,* 17(3), pp. 339-45.

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Method

1. Crystal for IN-LEDGF/p75 from the protein database
2. Construction of *in-silico* model of IN-LEDGF/p75 using AutoDock
3. Virtual screen of Zinc 15 against target
4. Top compounds selected and filtered using SwissADME
5. Best candidate selected for synthesis
6. Binding interactions mapped

Results

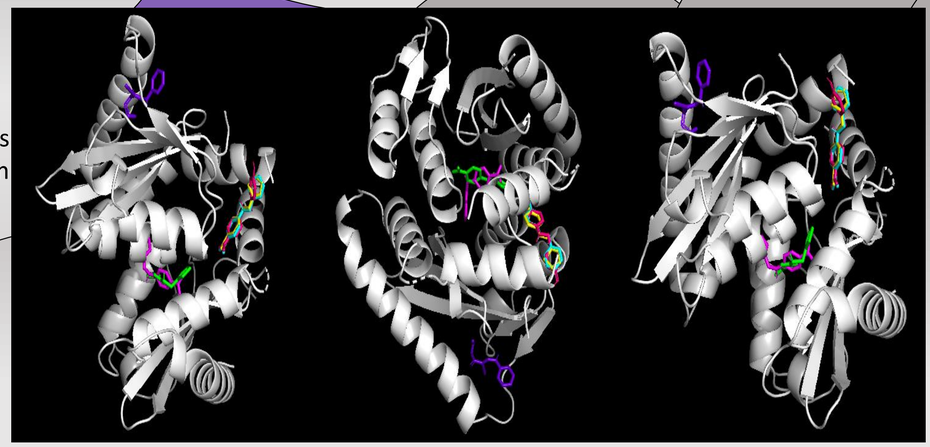

Figure 1. Three perspectives of the six various analogues binding to LEDGF/p75 (AutoDock). Yellow = 5-nitro-N-(thiophen-2-ylmethyl)pyridin-2-amine

Due to time constraints, synthesis of the selected integrase inhibitor was unable to be completed.

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.17 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: nitro_group, oxygen-nitrogen_single_bond
Leadlikeness	No; 1 violation: MW<250
Synthetic accessibility	2.29

Figure 2. Pharmacokinetic/druglikeness data of 5-nitro-N-(thiophen-2-ylmethyl)pyridin-2-amine from SwissADME.

Discussion and Conclusion

From running the six analogues via SwissADME and AutoDock, 5-nitro-N-(thiophen-2-ylmethyl)pyridin-2-amine was determined as the best compound for synthesis. This was based on the high GI absorption of the product which would allow for good oral bioavailability, the lack of selective cytochrome P450 inhibition which would cause few interactions, and also the druglikeness of the compound which follows Lipinski's rules, as exhibited in Figure 2. All these properties are important for a safe and efficacious oral drug delivery.

Further work would include finishing the synthesis of the compound, purifying the product and eventually testing the compound.