The identification and synthesis of allosteric integrase inhibitors.

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 cell¹. 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 genes². 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 DNA².

This project looked to develop novel small molecules capable of inhibiting the IN-LEDGF/p75 interaction.

Methods Crystal structure of IN-LEDGF/p75 obtained from PDB database In-silico model constructed in AutoDock and used to perform virtual screen. "hits" were selected based binding energy and 'druglike' properties

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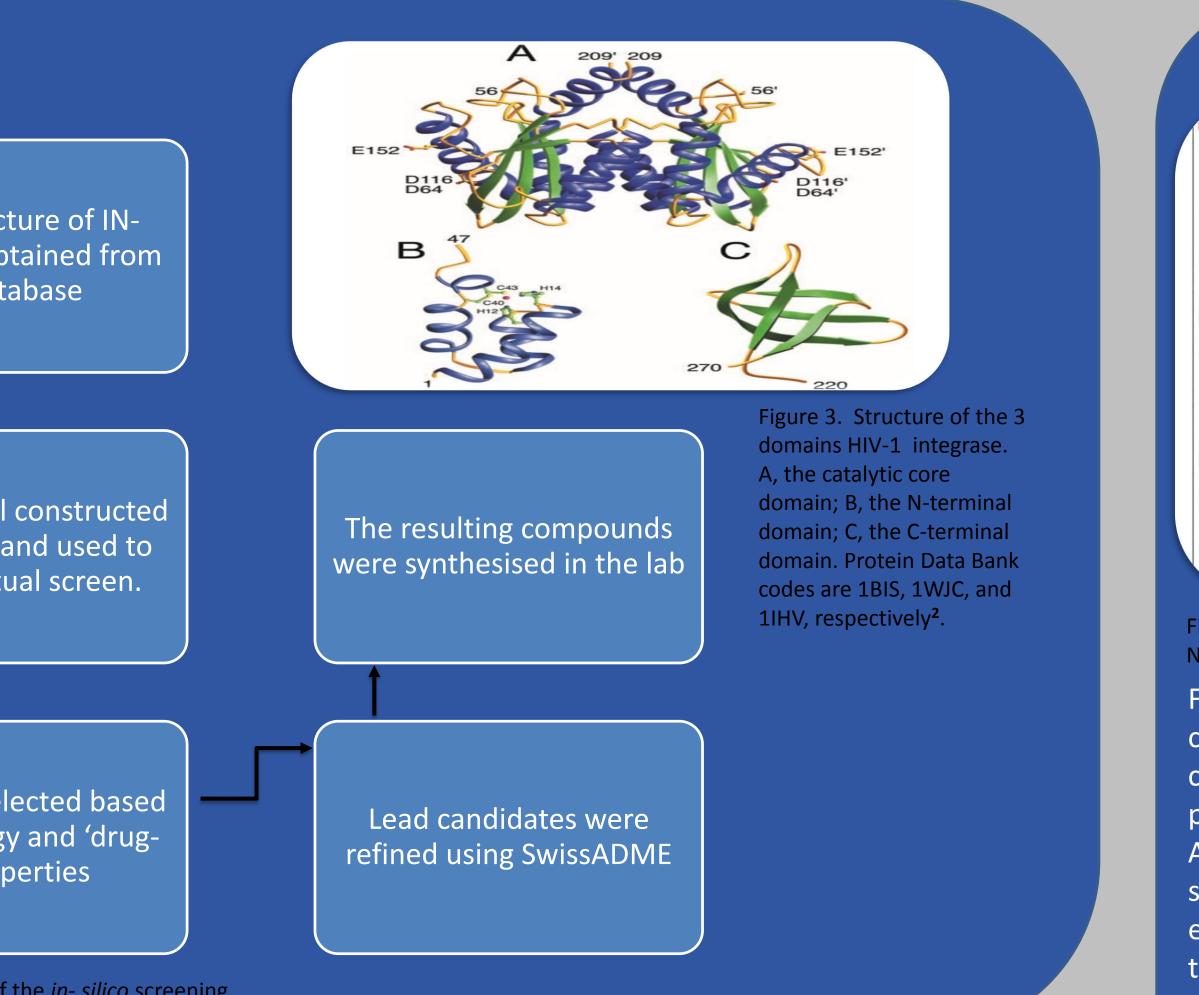


Figure 1: overview of the *in-silico* screening

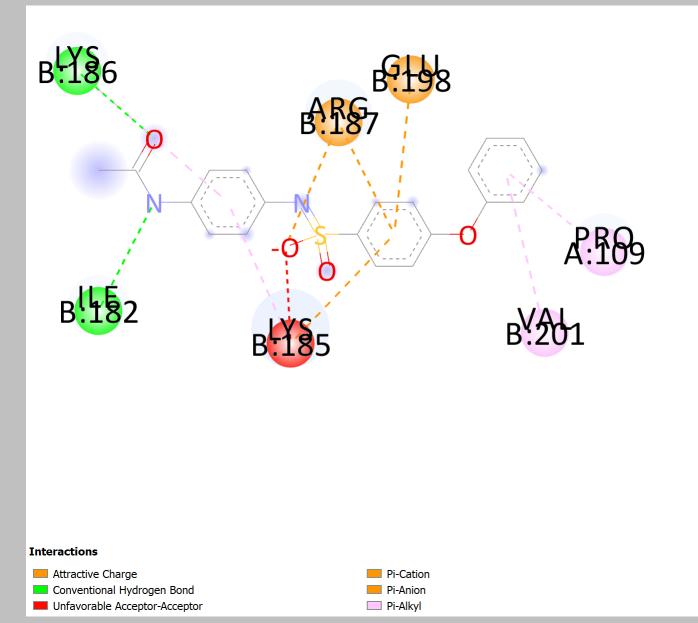


Figure 3. Structure showing the different binding interactions of N-[4-(4-phenoxybenzenesulfonamido)phenyl]acetamide.



Result

Molecule 1			
₩ @ @	H1 LIPO	Log S (ESOL) 😔 Solubility Class 📀	Water Solubility -4.09 3.08e-02 mg/ml ; 8.04e-05 mol/l Moderately soluble
	NH INSATU POLAR	Log S (Ali) Solubility Class Log S (SILICOS-IT) Solubility Class	-4.55 1.07e-02 mg/ml ; 2.80e-05 mol/l Moderately soluble -7.47 1.29e-05 mg/ml ; 3.37e-08 mol/l Poorly soluble Pharmacokinetics
SMILES CC(=O)Nc1ccc(cc1)NS(=O)(=O)c1ccc(cc1)Oc1ccccc1		GI absorption 🔨	High
Physicochemical Properties		BBB permeant 😣	No
Formula	C20H18N2O4S	P-gp substrate 🥹	No
Molecular weight	382.43 g/mol	CYP1A2 inhibitor 🥯	No
Num. heavy atoms	27	CYP2C19 inhibitor 🥹	Yes
Num. arom. heavy atoms	18	CYP2C9 inhibitor 10	Yes
Fraction Csp3	0.05	CYP2D6 inhibitor 69	Yes
Num. rotatable bonds	7	CYP3A4 inhibitor 😔	Yes
Num. H-bond acceptors	4	Log K _p (skin permeation) 6	-6.55 cm/s
Num. H-bond donors	2		Druglikeness
Molar Refractivity	104.38	Lipinski 🕖	Yes; 0 violation
TPSA 🥹	92.88 Ų	Ghose 🥹	Yes
	Lipophilicity	Veber 💿	Yes
Log Poly (iLOGP) 😣	2.10	Egan 0	Yes
Log Poly (XLOGP3)	2.94	Muegge 0	Yes
Log Poly (WLOGP) 😣	4.94	Bioavailability Score @	0.55
Log Poly (MLOGP)	2.59	Disuvaliability Goole 🐱	Medicinal Chemistry
Log Poly (SILICOS-IT)	2.27	PAINS (9	0 alert
Consensus Log Poly 0	2.97	Brenk 🖲	0 alert
		Leadlikeness 🥹	No; 1 violation: MW>350
		Synthetic accessibility 0	2.70

Figure 3. Pharmacokinetics properties of

N-[4-(4-phenoxybenzenesulfonamido)phenyl]acetamide³.

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.

References

2017;7(1).

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.

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