# The synthesis of novel HIV-1 RT inhibitors

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## Aims

- Identify a novel synthetic route to obtain potential HIV-1 RT inhibitors
- Synthesize novel analogues using the route developed
- Purify the analogues generated

## Introduction

Human immunodeficiency virus (HIV) was first identified 40 years ago and in 2020 it was estimated that 37.7 million (30.2–45.1 million) people were living with HIV (1).

HIV is a retrovirus that leads to immunodeficiency through the infection and destruction of cells involved in the immune system, with CD4 cells being particularly affected by HIV (2). Decreased CD4 cells can lead to potentially life-threatening, opportunistic infections which immunocompetent hosts would only rarely acquire (3).

A treatment regime known as highly active antiretroviral therapy (HAART) has been developed to shift HIV from a fatal condition to a chronic one (4). The aims of treatment are to improve the physical and psychological well-being of those infected by achieving an undeletable viral load, reducing transmission of the virus, maintaining immune function, decreasing mortality and morbidity associated with HIV whilst also reducing drug toxicity from HAART (4).

## The Project

Ongoing research and development of drugs against HIV is needed to overcome poor safety profiles in some combination medication regimes. Further research is also needed due to the highly adaptable nature of retroviruses and potential issues with patient adherence to HAART which can lead to drug resistance.

A route into overcoming these issues is being explored with a new cellular protein, eukaryotic translation elongation factor 1A (eEF1A). The enzyme reverse transcriptase (RT) is needed for replication and maintenance of long-term infection. eEF1A has recently been found to bind to RT ultimately facilitating replication of the virus. The project focused on the development and characterisation of compounds targeting eEF1A.

## Method

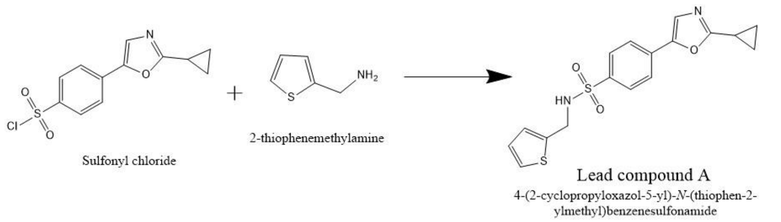


*Figure 1- A reaction scheme showing the synthetic route adopted to synthesize the lead compounds A and B*

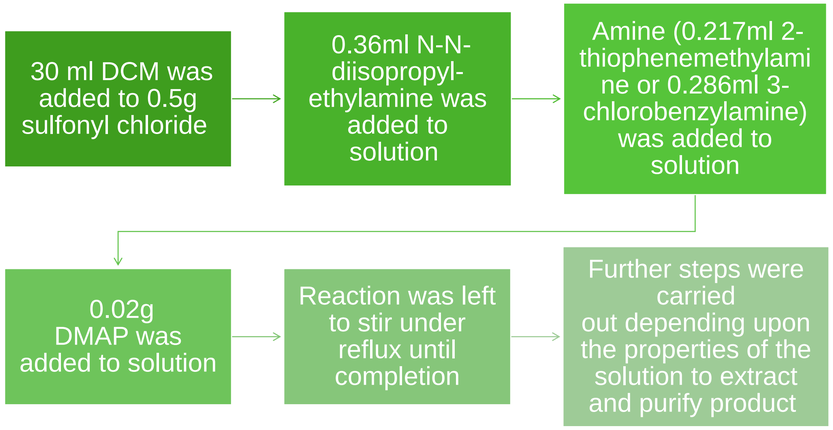


*Figure 2- The conditions of the standard synthetic route developed.*

## Results

- From the synthesized leads A and B, NMR data was generated to confirm the presence of functional groups, the purity and molecular structure of the compounds.
- Shown in figures 3 and 4, virtual screening of physicochemical properties of A and B showed that both compounds abide by Lipinski's rule of 5. This rule provides an indication that the compound will be suitable as an orally active drug in humans. Values of particular interest for compound A and B are:

Compound A: LogP 2.58, high GI absorption, impermeable to the blood brain barrier, bioavailability of 0.55 and soluble in water.

Compound B: LogP 3.39, high GI absorption, impermeable to the blood brain barrier, , bioavailability of 0.55 and moderately soluble in water.

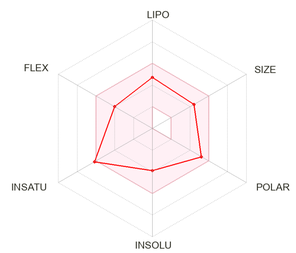


*Figure 3 – Predictive screening for the bioavailability of compound A*

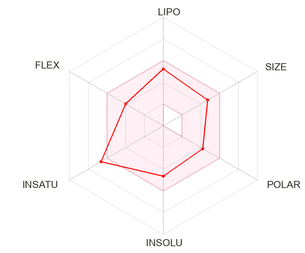


*Figure 4 – Predictive screening for the bioavailability of compound B*

## Conclusions

Analogues A and B were synthesized from the synthetic route developed, extracted and analyzed for their properties.

The analogues created in the project are to be sent off for biological testing to confirm their physicochemical properties and activity against eEF1A.

## Acknowledgements

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References: (1) HIV. [accessed 2 Oct 2022] Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-aids, (2) Vidya Vijayan KK, Karthigeyan KP, Tripathi SP, Hanna LE. Pathophysiology of CD4+ T-Cell Depletion in HIV-1 and HIV-2 Infections. Front Immunol. 2017;8:580. (3) Justiz Vaillant AA, Naik R. HIV-1 Associated Opportunistic Infections. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. [accessed 2 Oct 2022] Available from: http://www.ncbi.nlm.nih.gov/books/NBK539787/, (4) Committee, Joint Formulary. BNF 80 (British National Formulary). London: Pharmaceutical Press; 2020. p 677