Synthesis of allosteric reverse transcriptase inhibitors targeting the HIV-1 virus

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Introduction

Human immunodeficiency virus - 1 (HIV-1) impairs and destroys the immune system cells resulting in a gradual immunodeficiency culminating in the most severe stage of acquired immunodeficiency syndrome (AIDS) (1).

As of 2021 globally there was 38.4 million people living with HIV, with 1.5 million new infections in 2021 alone and 650,000 people died from AIDS related illnesses in 2021 (2).

HIV-1 has been suppressed through the use of highly active antiretroviral therapy (HAART) which suppress the viral replication but does not provide a cure (1).

This project focusses on targeting reverse transcriptase which is one of three viral enzymes required for successful viral replications. Targeting this enzyme could provide an innovative way to stop HIV replication, helping to treat the disease.

Aims

The aims of this medicinal chemistry project are:

- Synthesis of novel reverse transcriptase allosteric inhibitor analogues
- Record and identify optimum reaction conditions and methods
- Prepare samples for biological testing
- Evaluation of physiochemical properties for drug developments

Methodology

A virtual screening programme using a RT-eEF1A complex model has led to the identification of small molecule leads that can disrupt the protein-protein interaction and hence potentially disrupt viral replication.

Image 1 shows a computer model generated as part of the study, in which reverse transcriptase (blue and yellow) binds to the DNA strand (red and green). The molecules generated by this study intend to inhibit this process.

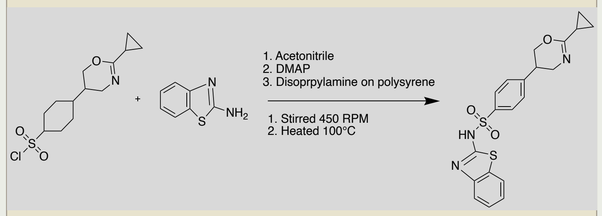


Image 2

Novel analogues were then synthesized by the method shown in the reaction scheme (image 2); varying the amines allowed the generation of novel leads.

The drugs produced were then obtained by varying recrystallisation methods according to their specific physiochemical properties

Results

Image 3 shows 6 novel analogues of varying yields and purities that were synthesized with repeat batches made of those with lower yields to allow enough sample for further analysis.
Image 4 shows the physiochemical data collected for this molecule

Image 4

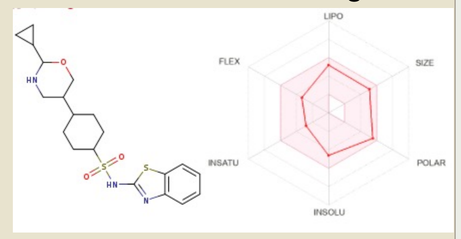


Image 1

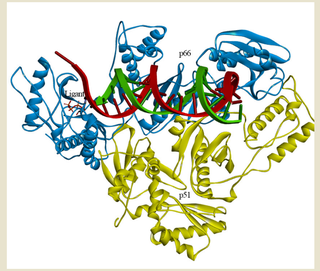
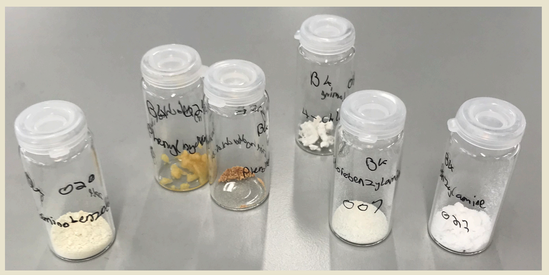


Image 3



Conclusions

This piece of research concluded successfully with the goals of the project being fulfilled. The project resulted with:

- Successfully evaluated a new synthetic route to obtain multiple benzenesulfonamide analogues
- Developed methods to obtain compounds in sufficient purity
- Analysed the physiochemical properties of the products obtained
- Future aims of this research are to send the products synthesised through to biological screening

Acknowledgements
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References
1. WHO HIV – WHO HIV factsheet 27//07/2022
2. Global HIV and AIDS statistics - UNAIDS Fact sheet 2022