Development of new allosteric HIV-1 Reverse Transcriptase Inhibitors

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1. Introduction

In 2019, 38 million people were living with HIV. In 2019, 25.4 million people were accessing antiretroviral therapy. In 2019, 690,000 people died of AIDS-related illnesses. (1)
HIV is normally treated using combination therapy- normally three drugs, often combined into one medicine. This treatment does not cure HIV, but it stops the virus from reproducing within the body, leading to a very low volume of virus- an undetectable level- meaning that HIV cannot be passed on. Antiretroviral therapy can lead to a normal or near-normal lifespan for people who are accessing it. (2) Therefore, access to antiretroviral therapy is key to achieve the Sustainable Development Goal Target 3.3 to end AIDS by 2030.

This project was to identify, synthesise and collect information on new small molecule leads, that could disrupt protein interactions within an enzyme in the HIV virus, which could stop their replication. These small molecules could be developed into new HIV drugs, used in combination with existing drugs to improve access to antiretroviral therapy.

Aims:
- Synthesis, characterisation, and evaluation of the physiochemical properties of one of the lead compounds
- Identification of an appropriate compound to be prepared for biological testing

2. Method

General Method:
1. 1 equivalent of sulfonyl chloride and dichloromethane (17 mL/mmol) were added.
2. 1. 2 equivalents of N,N-diisopropylethylamine were added in a single step.
3. 1.2 equivalents of the amine were added in a single step.
4. 0.1 equivalents of 4-dimethylamineopyridine was added in a single step.
5. Suspension heated at 40ºC overnight
6. TLC was undertaken to ensure reaction was complete (1:4 ethyl acetate : petroleum ether)
7. Product vacuum filtered and evaporated to dryness
8. 5mL of ethyl acetate was added and the suspension was stirred at room temperature
9. Product was evaporated to dryness
10. 5mL of ethyl acetate and 5mL of petroleum ether was added
11. Product was evaporated to dryness
12. 3mL of acetone added, placed into an ice bath and stirred for 15 minutes
13. Product was filtered

Note: this method was adapted depending on which amine was used.

3. Results

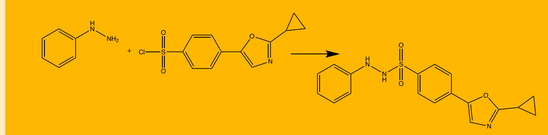

Figure 3.1: The reaction scheme of phenylhydrazine hydrochloride and 4-(2-cyclopropyl-5-oxazolyl)benzene sulfonyl chloride, to produce 4-(2-cyclopropyloxazol-5-yl)-*N'* Phenylbenzenesulfonohydrazide.

Figure 3.1 shows one of the reactions undergone to produce a potential new allosteric HIV-1 Reverse Transcriptase Inhibitor. This inhibitor was selected to be included in results because from calculations, 4-(2-cyclopropyloxazol-5-yl)-*N'* Phenylbenzenesulfonohydrazide adheres to all Five of Lipinski's rules, as well as the rules of Veber et al. This means that it is highly likely to be orally active- meaning that it will work as a drug that can be ingested. Therefore, it is a good candidate to go forward for biological testing, and into clinical trials. (3)

From ^{1}H NMR data, 4-(2-cyclopropyloxazol-5-yl)-*N'* Phenylbenzenesulfonohydrazide has been produced, however some impurities can be identified.

4. Conclusion

In conclusion, 4-(2-cyclopropyloxazol-5-yl)-*N'* Phenylbenzenesulfonohydrazide has been successfully synthesised and identified as an appropriate compound to be prepared for biological testing.

Should this compound show promise with biological testing, it may be made into a medicine, by adding necessary excipients to stabilize it and allow it to work within the body. It would then undergo rigorous clinical trials, ensuring that there are no serious adverse effects, and that the drug works as expected. These clinical trials could take upwards of ten years.

From the ^{1}H-NMR data of 4-(2-cyclopropyloxazol-5-yl)-*N'* Phenylbenzenesulfonohydrazide has been produced, however has some impurities. Therefore, the method should be further developed in order to produces a more pure compound for future testing.

Future aims:
- The compound should be prepared for biological testing.
- The method should be developed further in order to increase purity.

5. References

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6. Acknowledgements

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