

Synthesis of Photodegradable Antibiotics

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Introduction

Fleming's discovery of penicillin in 1928 revolutionized modern medicine in its ability to treat infections¹. Millions of lives have been saved since it was first introduced, which consequently extended the average human lifespan by 23 years². Despite its successes in being an effective and life saving form of treatment, it has simultaneously created a new problem that is increasingly affecting both our health care, agriculture and wildlife. This especially affecting our marine environment¹. Multi-drug-resistant bacteria (MDR), has made it increasingly difficult to treat infections with antibiotics. In 2019, 1,27 million people passed due to antibiotic resistance, by 2050 WHO estimates that 10 million people will die annually due to antibiotic resistance³. A patient treated with antibiotics can excrete as much as 90% of the active substance, this excretion ending up in wastewater and subsequently in the ocean⁴. This is important not only because it affects marine life, but also the seafood we ultimately consume⁴. There is a need overall for greener pharmaceuticals as this type of pollution is not exclusive to antibiotics, however with the increasing threat of antibiotic resistance, it is the focus of this project. This project aims to create a new form of antibiotics, that under the exposure of UV-light will break down into low- or non-toxic inactive compounds⁴. This will hopefully in the future reduce both marine pharmaceutical pollution as well as slow down antibiotic resistance³. This project develops several scaffolds of antibiotics, but here we will focus on triazole-based antimicrobial agents with variations of functional groups connected to the aromatic. These variations consists of a fluoro-derivative, a cyano-derivative and a methoxy-derivative.

Method

All three variations underwent the exact same 4-step synthesis, being ultimately obtained by a "click-reaction". TLC, NMR and IR was used to confirm that the desired products had been obtained and that the products obtained were pure. TLC is also to be used during the UV degradation test to confirm the scaffolds breaking down forming new compounds.

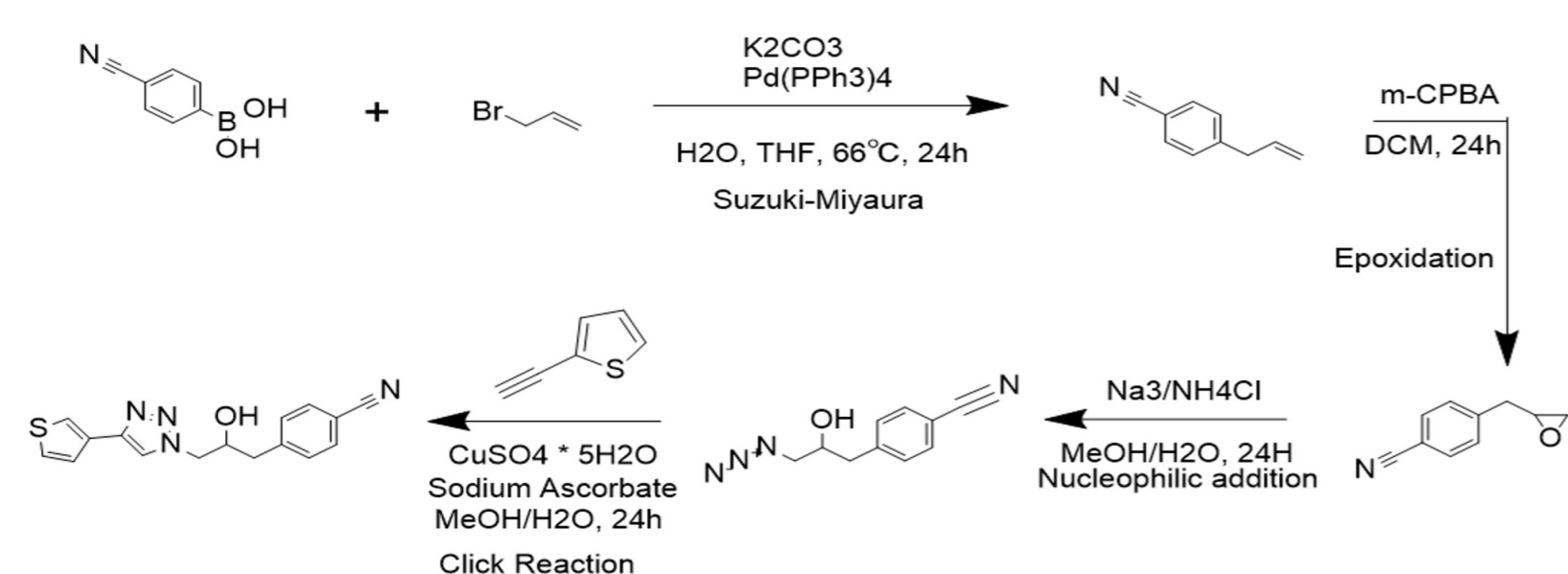


Figure 1.2 Synthesis of cyano-derivative

Results and Discussion

The synthesis of these 3 different triazole-based compounds despite following the exact same procedure, showed varied stability during the various steps. The methoxy especially proved to be quite unstable up until the click reaction. The reaction time was in addition significantly longer, even when applying a higher equivalent of the palladium catalysts, it still required additional hours, and during the epoxidation step, additional days to fully react, when compared to the average reaction times of the fluoro- and cyano-derivatives. The cyano-derivative was significantly more stable compared to the fluoro and methoxy derivatives. These functional groups significantly affect the synthesization process of this type of triazole-based antibiotic. UV degradation proved unfruitful after the first attempt using a vessel carrying high volumes of solution. The methodology was then switched to using individual NMR-tubes, which also made testing several compounds at once possible. Each compound showed to have degraded within an hour, but testing its degradation times within that hour, proved difficult as the UV-lamp ended up breaking. Further tests of these compounds will be needed in the future.

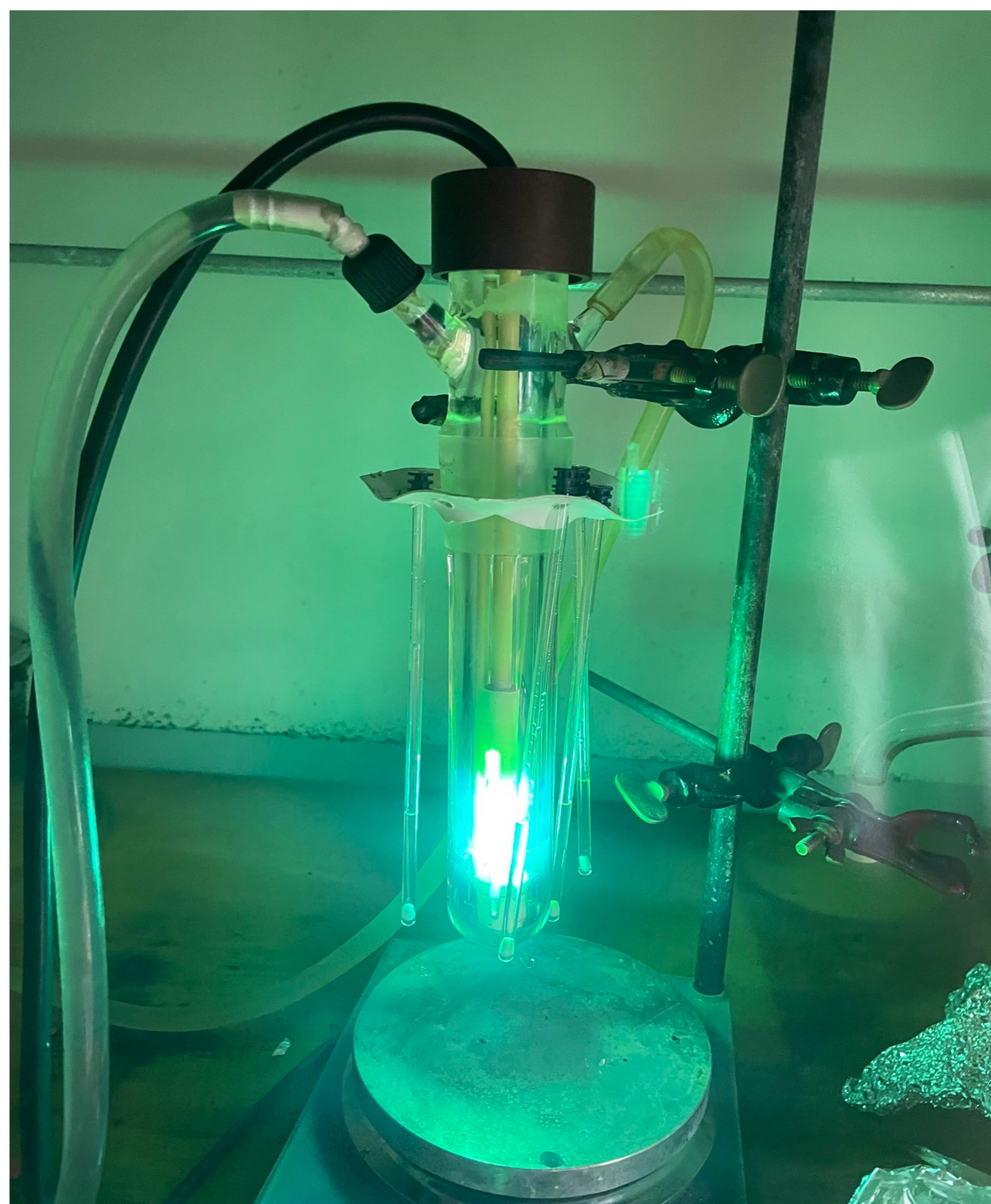


Figure 1.1 UV degradation testing using the new NMR-methodology

Derivative type	Degradation time
Methoxy	1h
Fluoro	1h
Cyano	1h

Table 1.1 Degredation times and amount of resulting new compounds



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