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DESIGN OF ANTIBACTERIAL MOLECULES BY PHOTOPHARMACOLOGY (ECOPHOTOSKIN)

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Abstract

Antibiotics are rejected in the environment after their use for treating human and animal bacterial infections. These residues are poorly eliminated by the actual wastewater treatment processes, impacting both animal, human and environmental health. This led to the emergence of antibiotic resistance in bacterial pathogens. To fight this issue, the last decades have been marked by the apparition of photopharmacology. This approach based on the use of the light is a promising way to control the antibiotic activity of a drug. Indeed, under a UV light irradiation, the drug is activated and exercises its antibacterial activity. In contrary, when the drug is released in the environment, its visible light illumination enables its deactivation. Thus, this work proposes the design of antibacterial molecules to be used for photopharmacology to treat bacterial infections.

Key words: photopharmacology, antibacterials, medicinal chemistry, physicochemistry.

I- Introduction

Antibiotics are commonly used to treat animal and human bacterial infections. However, their overuse is a source of concern due to the development of a high bacterial resistance stemming from the accretion of antibiotics in the environment.(1) Thus, it is necessary to find a strategy to limit this antibioresistance according to the “one health” concept which is an approach that recognizes that the human health is closely connected to the animal health and the environmental health.(2) Hence, the use of light appears to be a promising strategy to control the drug activity in order to limit the antibiotic resistance from bacteria. This approach called photopharmacology offers a high level of spatiotemporal resolution and is generally non-invasive.(3) This concept is based on the introduction of a light-sensitivity into a drug through functionalization with bistable molecular photoswitches.(4) Among them, azobenzenes are the most used photoswitches and undergo a reversible change of their structures and properties, upon the absorption of a photon.(4-5) Thus, under a UV

light irradiation, the photoswitch isomerizes from its *trans* conformer to its *cis* conformer, activating the drug activity. In contrast, under a visible light irradiation or by heating, the *cis* conformer isomerizes into the *trans* conformer, disactivating the drug activity (Figure 1). (6–8) Triazenes are molecules of pharmaceutical interest (9) which can be used as molecular photoswitches. As well as azobenzenes, triazenes can also isomerize under a UV light irradiation from its *trans* conformer to its *cis* conformer enabling the activation of the drug activity (Figure 1). Conversely, by an exposure to the visible light, or by heating, the *cis* conformer isomerizes into the *trans* conformer, leading to the deactivation of the drug activity.

Although the coupling between photoswitches and antibiotics is recent, it has been used to fight bacterial antibiotic resistance. For instance Feringa et *al* (10-11) have demonstrated the efficiency of a modified-trimethoprim on bacterial growth inhibition in *E.coli*. They also worked on fluoroquinolone antibiotics on which they have graft azobenzene photoswitches (12-13) to test coupled molecules on bacteria. Similarly, our work is based on the synthesis of compounds formed by coupling a photoswitch and an antibiotic. Then, we tested these molecules on *E. coli* to evaluate their antibacterial activity without UV light irradiation.

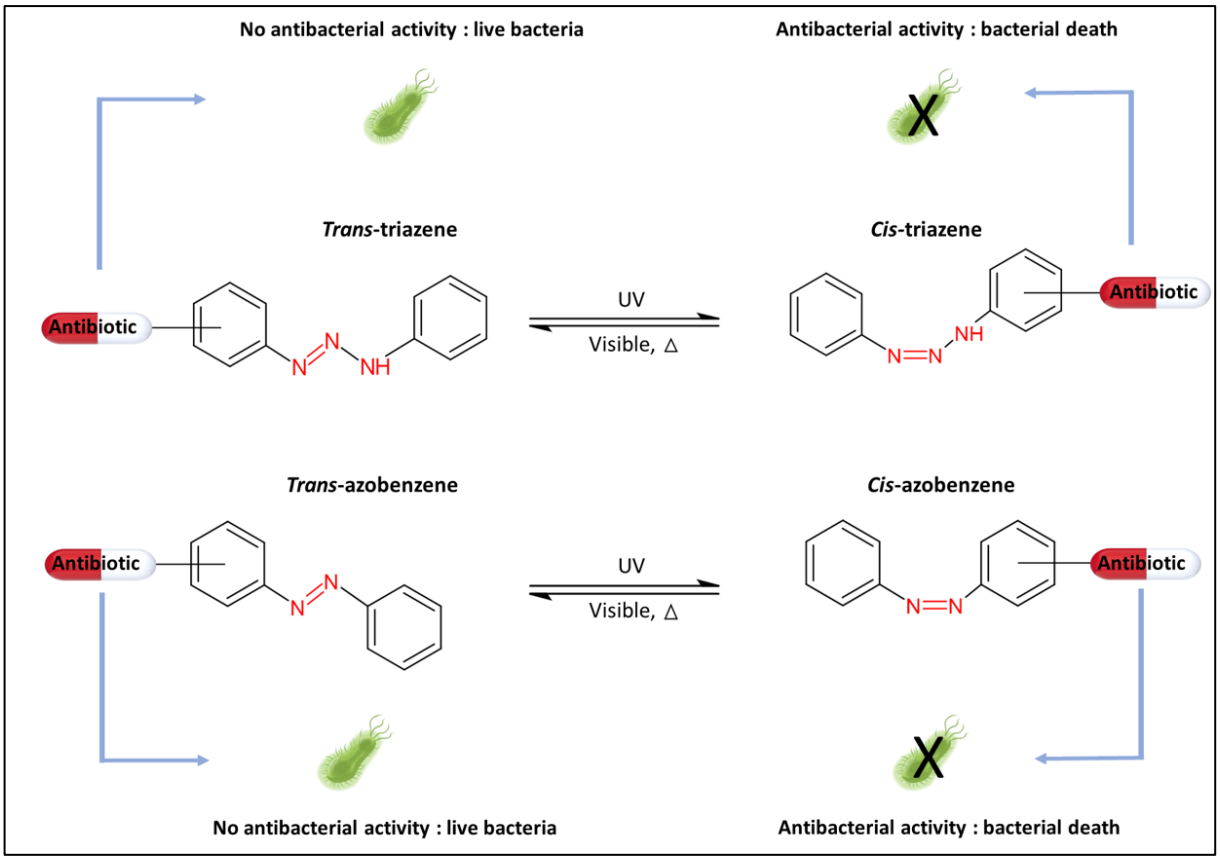

Figure 1: Process of isomerization of molecular photoswitches.

II- Results

The step of coupling compounds synthesis enabled the obtainment of a panel of 70 molecules which are divided into three families:

- Azobenzene-antibiotic family
- Triazene-antibiotic family
- Azobenzene family

The antimicrobial activity of all compounds has been evaluated against an *E. coli* strain without UV light irradiation. The results of screenings are presented in the form of histograms illustrating the percentage of the bacterial growth inhibition for each compound at a concentration of 50 mg/L.

Among the compounds of the azobenzene-antibiotic family (Figure 2), compounds **1** to **6** have shown a lack of antibacterial activity on *E. coli* apart from the first compound. However, this compound has reached an inhibition of only 10% of the bacterial growth without UV light irradiation. Moreover, the compounds **11** and **14** have shown an antibacterial activity of 88% and 96% respectively on *E. coli*. Furthermore, the other compounds of this family have presented an antibacterial activity between 17% (compound **8**) and 64% (compound **10**). Thus, all of compounds, except compounds **11** and **14**, will be interesting to verify the impact of the UV light irradiation on antibacterial activity.

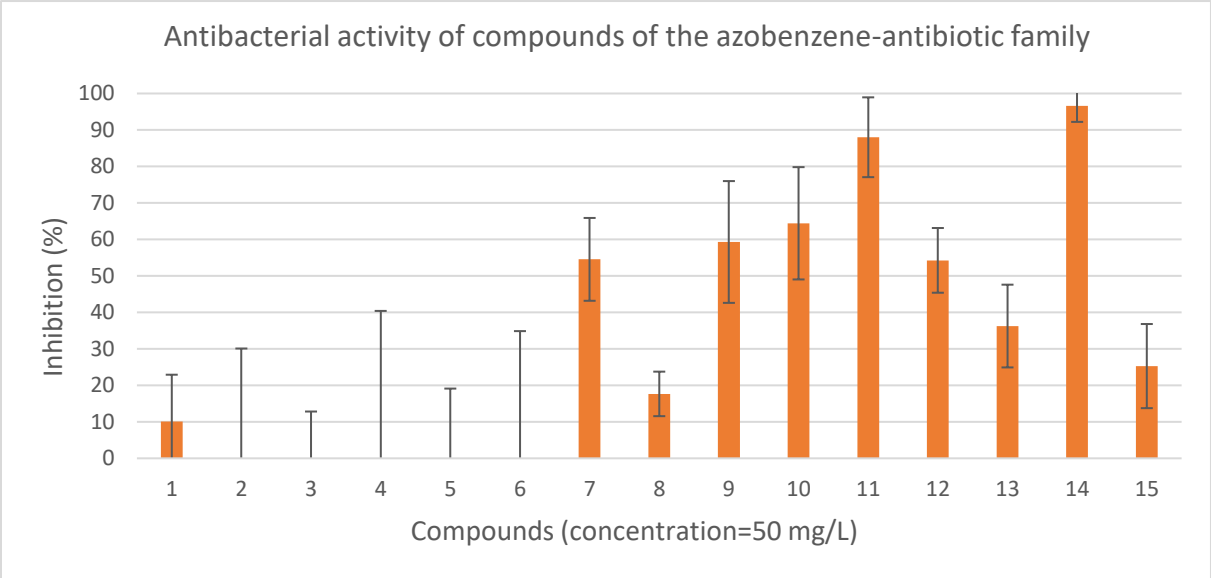

Figure 2: Histogram showing the inhibition of bacterial growth for each compound of the azobenzene-antibiotic family.

The azobenzene moiety has been tested alone to verify if the antibacterial activity of compounds belonging to the azobenzene-antibiotic family was due to the photochrom only or was due to the entire molecule. The antibacterial activities of photochroms were lower than 20% or neutral except for the compound **64** (41% of inhibition) and the compound **66** (32% of inhibition) (Figure 3). This confirmed that the antibacterial activity of azobenzene-antibiotic compounds not came from the photochromic moiety.

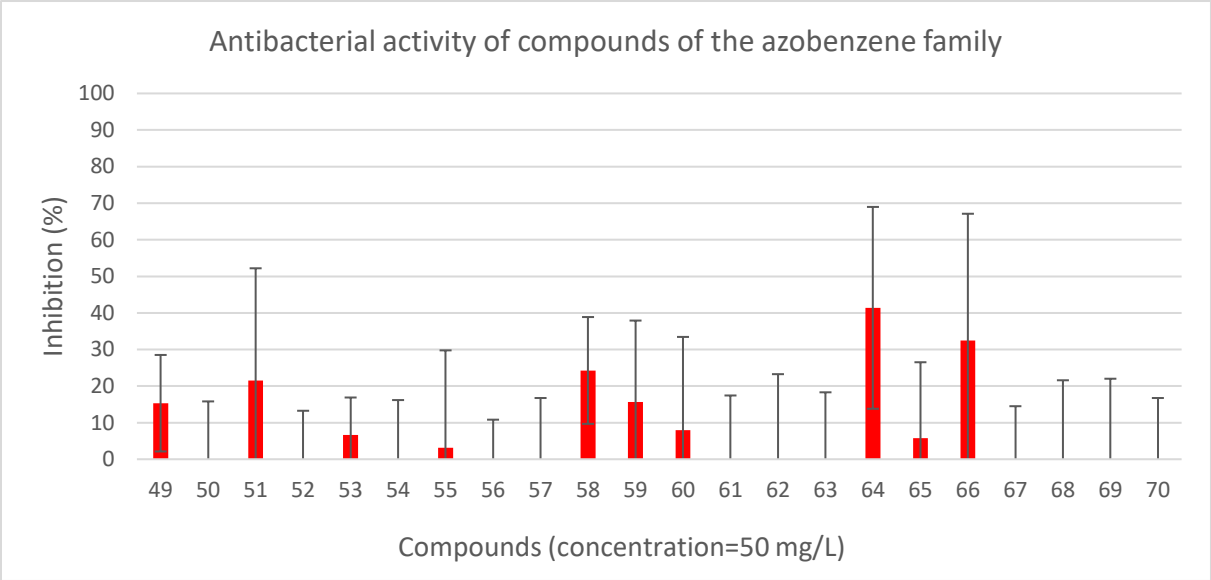

Figure 3: Histogram showing the inhibition of bacterial growth for each compound of the azobenzene family.

The compounds of the family triazene-antibiotic were very efficient on *E. coli* without UV light irradiation. The majority of compounds have inhibited over 70% of the bacterial growth. However, compounds **26**, **27, 40, 41** and **42** have shown an antibacterial activity between 40% (compound **42**) and 57% (compound **27**). In addition, the compounds **24**, **43**, **44**, **45** and **47** have shown an antibacterial activity between 10% and 30%. As for the compounds **46** and **48**, their percentage of bacterial growth inhibition was lower than 10% (Figure 4). Thus, compounds with a percentage of bacterial growth inhibition between 0% and 70% will be very interesting to estimate the contribution of UV light irradiation on antibacterial activity.

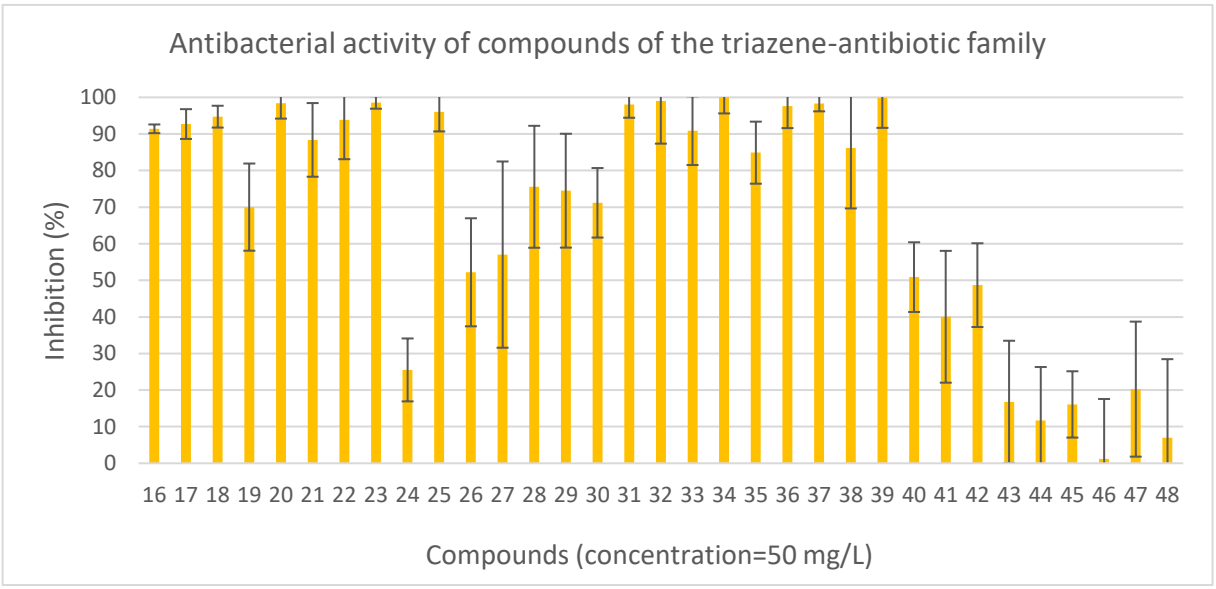

Figure 4: Histogram showing the inhibition of bacterial growth for each compound of the triazene-antibiotic family.

III- Conclusion and perspectives

The 70 compounds belonging to three different families were obtained throughout the organic synthesis step. Then, these compounds have been tested on *E. coli* without a UV light irradiation. On the one hand, from this screening, most triazene-antibiotics have shown excellent antibacterial activities on *E. coli*. However, five compounds have presented a medium inhibition (40-60%) and seven compounds have shown a bacterial growth inhibition less than 30%. On the other hand, two compounds of the azobenzene-antibiotic family have also shown a high antibacterial activity on *E. coli* without a UV light irradiation. However, the other compounds belonging to this family have reached a percentage of inhibition lower than 62%. Furthermore, compounds **1** to **6** were inactive or weakly active on *E. coli*.

Consequently, it will be very interesting to test all compounds on *E. coli* with a UV light irradiation in order to measure its impact on antibacterial inhibition. Finally, azobenzene photoswitches were tested on *E. coli* without a UV light irradiation. The majority of the photoswitches have shown a lack of activity or an activity lower than 40%. These results proved that the antibacterial activity of azobenzene-antibiotic compounds not came from the azobenzene moiety. Thus, it will be important to achieve tests in attendance of a UV light irradiation to identify the impact of the photochromic isomerization on the inhibition of the bacterial growth on *E. coli* and evaluate the safety of the process for human cells.

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