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Photoresponsive antibiotics and cytotoxic agents

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Sitkowska, K. D. (2019). *Photoresponsive antibiotics and cytotoxic agents: On the use of light for the advancement of medicine and the knowledge of living organisms*. University of Groningen.

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Conclusions and Future Prospects

Conclusion

The use of light in biological applications has been continuously growing in the past years. In the field of applied medicinal chemistry, the burgeoning interest in the potential of photopharmacology has recently turned it into a fully-fledged field, driven by many groups from which many interesting advances have emerged.

Remarkably, the success of this field was powered by a very simple energy source, light. The properties of light, such as its great spatial and temporal resolution using irradiation, negligible toxicity in the therapeutic window range and bioorthogonality towards most of the processes in the living bodies, make it an alternative and readily available tool. For example, its use has already allowed the preparation of selectively activated drugs and probes for the visualization of diseases.

In this thesis, the development of novel applications of light was described through the synthesis and implementation of light-responsive compounds for diverse medically-relevant purposes. Initially we prepared new green-light-sensitive photoprotecting groups based on BODIPY dyes, with the purpose of using them to create protected, deactivated drugs, for safer and more precise delivery to zones needing treatment. These compounds evolved then into more biologically friendly red-light-sensitive PPGs, which were applied to carry and release two well-known drugs. The tests performed on the resulting protected Mitomycin C, a commonly used chemotherapy agent and Neomycin, an antibiotic, demonstrated the principle behind the idea of using light to deliver drugs in this fashion to counter the adverse effects of chemotherapy and bacterial resistance.

While the compounds could be successfully obtained, after optimization, via a new, robust, synthetic pathway which overcame many synthetic problems, the release of the carried compounds proved less straightforward than anticipated. Indeed, BODIPY protected Mitomycin C degraded instead of deprotecting pushing us to reconsider our design in this case. On the other hand, we were positively surprised that, after some effort, the release of *o*-nitrobenzyl protected Neomycin C proceeded smoothly and yielded the carried drug cleanly which still acted at full

efficiency. Overall these two examples showed how key the choice of where to attach our carriers to the drugs is. We now believe that our method could readily be applied to prepare other BODIPY-Mitomycin C derivatives that would function as initially planned.

Successful results were also obtained with our newly prepared BODIPY-based probes for detecting ROS. Initial experiments suggest that these probes do react in the desired manner when in the presence of ROS, validating our design. While the exact mechanism of their action was not proven, we believe that the robustness of our new synthetic pathway will allow us to further hone these probes into useful tools.

In our opinion, the work described in this thesis represents a proof of concept of our approach based on BODIPY carriers and a stable basis upon which to continue building new, more efficient, photoprotected drugs of this type and upon which the field of using light in biological applications will further expand. With the information obtained from the Mitomycin C, Neomycin and ROS probe systems, we now have a clearer idea of how to design the next generation of compounds which should show better properties respectively in terms of how they are released, in terms of inhibiting the activity of carried drugs, and in terms of their fluorescence properties, all which remain key challenges to overcome before these methods can become applicable. These new designs can be realized in a manner not possible beforehand via the application of our new methods.

Future prospects

Cancer and the growth of bacterial resistance are among the most important health problems of today's society. Even though the solution this thesis elaborates upon, which is using light combined with photosensitive moieties integrated into the structures of drugs or probes to maximize their effectiveness while dampening side effects, is seeing a significant raise in attention and has, included via this thesis, already provided promising initial results, there is still a lot to be discovered before these new tools become fully mastered and usable on a daily basis in medicine.

For example, there are still processes linked to ROS for which biological markers are not yet known. If these were known, new efficient fluorescent probes could be developed for their visualization which would help to understand the nature of these processes and their implication in biological pathways and diseases. In this problem lies the biggest challenge for future advances. As what is known is, at best, a source of heavy debate between experts in the field, there is little reliable evidence on which to base the design of new probes. As unsuccessful research is rarely published, one can only speculate, based on one's personal experience, in the field how many approaches to the problem have failed. However, better understanding of these processes remains vital for future medical development. Therefore, dedicated effort via a trial and error approach must be continuously applied to the problem until better footholds towards understanding this process are obtained. While our probes, designed and optimized in this manner, represent a novel, successful, foothold to tackle this problem in a manner not possible before, with early results showing much promise, they remain understudied and more measurements on dummy systems are needed to fully characterize them before they can be used to study living systems.

Similarly, the field of photopharmacology, albeit holding many promises for yielding selective drugs as demonstrated within this thesis, still lacks definitive guidelines of how to successfully incorporate either molecular switches or photoprotecting groups into drug structures to attain the desired photocontrol of their activity. This is in part due to a limited understanding of how functional groups are involved in the activity of drugs. Many studies will just characterize changes in activity when a group is altered but do not explore the exact reason why these changes occur. It becomes therefore hard to judge what influence adding a photosensitive moiety to one would have in terms of inhibiting drug activity. These limitations are responsible for lowering the success rate of the conducted research and making the trial and error approach as successful as any design-driven research demonstrating the need for better fundamental understanding of the drugs SAR before the field can be furthered in an applied sense.

Another, unaddressed, yet considerable challenge for photopharmacology is the lack of readily available light irradiation systems which could be employed in hospitals. With the used λ_{max} of irradiation ranging from 300 to 700 nm, one can

imagine the difficulty of designing error-resistant machines fit for clinical uses combining all needed functionalities.

Also, with the trend of designing moieties sensitive towards light of longer wavelengths, to counter the adverse effects linked to the use of UV light, new strategies are also needed for the preparation of such compounds, as the known ones come with their own limitations. Substitution on the aromatic rings of the fluorophores causes a change in their electronic properties, potentially leading to a different switching or cleavage behaviors, which, in extreme cases, can result in the loss of the desired properties. Extending the π systems of the chromophores usually leads to the increase of the size of the molecule and decreases its solubility in aqueous media, posing another formulation problem. This could cause new compounds, ideal in their properties and behavior *in vitro*, to precipitate in biological environments, rendering the drugs useless *in vivo*. To address these emerging problems the pharmacokinetics of these compounds need to be taken more into account as it has been greatly ignored in favor of pharmacodynamics and the moieties being integrated need to be complexified to take both into account by for example developing moieties capable of extending π systems while increasing solubility via further substitutions.

With these challenges in mind, there are still a lot of questions that need addressing before the field of using light in biological applications can truly progress, be it in photodynamic therapies, fluorescent sensing or optigenetics. A step back to study the fundamentals involved more thoroughly is needed before the applications, which many seem overly eager to rush into, can be truly considered. If these are solved one day, however, this methodology will provide applications that would become invaluable tools in the battle against bacterial resistance and cancer.