Polycationic Silicon Phthalocyanines as Photosensitizers for Photodynamic Therapy and Photodynamic Inactivation of Microorganisms

Eveline van de Winckel, Andrés de la Escosura, Tomás Torres

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, España
eveline.vandenwinckel@uam.es

Abstract

Photodynamic therapy (PDT) is a form of therapy that uses light-sensitive compounds, which upon selective exposure to light become toxic to targeted malignant and other diseased cells [1]. Since its incidental discovery in 1900, photodynamic therapy (PDT) and all related aspects, ranging from its mechanism of action, the different photosensitizers that can be employed and its clinical applications have been studied in great detail.

In general, it is well-known that three components are required for PDT to occur; a photosensitizer, oxygen and a light source. In the presence of oxygen, irradiation of the photosensitizer of choice can lead to the generation of singlet oxygen, which is a powerful, indiscriminate oxidant that reacts with a variety of biological molecules. Singlet oxygen is indeed the main reactive oxygen species (ROS) in PDT, responsible for the destruction of tumor cells, bacteria, viruses, etc. [2]. Following the absorption of light, the photosensitizer is transformed from its ground singlet state (S0) into an electronically excited triplet state (T1) via a short-lived excited singlet state (S1). The excited triplet can undergo two kinds of reactions as shown by the Jablonski diagram depicted in Fig 1. Firstly, it can participate in an electron-transfer process with a biological substrate to form radicals and radical ions that, after interaction with oxygen, can produce oxygenated products (type I reaction). Alternatively, it can undergo a photochemical process known as a type II reaction, which results in the conversion of stable triplet oxygen ($^3O_2$) into the short-lived but highly reactive singlet oxygen ($^1O_2$) species, the putative cytotoxic agent.

Phthalocyanines are an important class of non-natural organic pigments that have received considerable attention in the field of PDT [3].Our focus will be centered on the design of novel silicon phthalocyanines with different substitution patterns in their axial positions (Fig 2) as new photosensitizers for their use in photodynamic therapy. For different and multipurpose reasons, it has been chosen to incorporate a series of polyamine ligands on one face of the phthalocyanine core, while on the other face a series of hydrophobic ligands are incorporated. In this way, the obtained photosensitizer molecules will be amphiphilic, which is a desirable characteristic to facilitate their possibility to cross cell membranes and improve their cell uptake. Another reason to incorporate various polyamine chains in one of the ligands is the fact that under physiological pH these polyamine chains will be protonated. This is useful to target Gram negative bacteria, which, in contrast to Gram positive bacteria that only possess an inner cell membrane and peptidoglycan layer, also possess an outer negatively charged cell membrane. For this reason, for the photosensitizer to be able to cross this membrane it is required to be positively charged. Furthermore, polyamines are naturally occurring compounds that play multifunctional roles in a number of cell processes including cell proliferation and differentiation. Rapidly dividing cells such as tumor cells require large amounts of polyamines to sustain the rapid cell division. Part of these materials can be biosynthesized internally, while the majority is imported from exogenous sources through active and specific polyamine transporters (PAT). These features have led to the use of polyamines as potent vectors for the selective delivery of chemotherapeutic and DNA-targeted drugs into cancer cells [4].

In summary, we have designed and are currently preparing a library of ligands to incorporate in the silicon (IV) phthalocyanines, making use of different substitution patterns in their axial positions. An overview of the series of ligands to incorporate can be seen in Fig 2. The resulting amphiphilic phthalocyanines are expected to be non-aggregated in aqueous media, because of their axial substituents, and are expected to have an enhanced photoinduced singlet oxygen generation in the pH range from 5 to 7.

References

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Figures

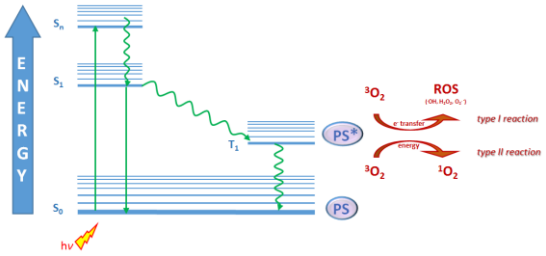

Fig 1. Jablonsky diagram that illustrates the photophysical and photochemical processes occurring when a photosensitizer (PS) is irradiated for PDT purposes.

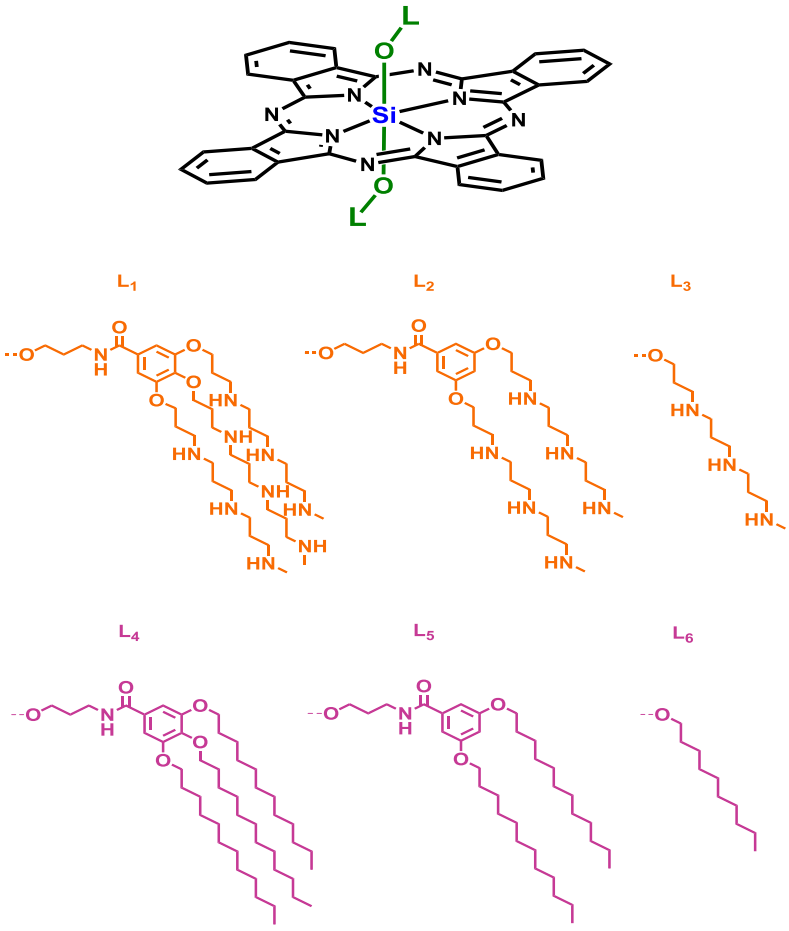

Fig 2. General structure of novel silicon phthalocyanine photosensitizers with different substitution patterns in their axial positions, and a representation of several of the ligands to be incorporated (top: series of polycationic ligands, bottom: series of hydrophobic ligands)