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Trends and targets in antiviral phototherapy

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Photodynamic therapy (PDT) is a well-established treatment option in the treatment of certain cancerous and pre-cancerous lesions. Though best-known for its application in tumor therapy, historically the photodynamic effect was first demonstrated against bacteria at the beginning of the 20th century. Today, in light of spreading antibiotic resistance and the rise of new infections, this photodynamic inactivation (PDI) of microbes, such as bacteria, fungi, and viruses, is gaining considerable attention. This review focuses on the PDI of viruses as an alternative treatment in antiviral therapy, but also as a means of viral decontamination, covering mainly the literature of the last decade. The PDI of viruses shares the general action mechanism of photodynamic applications: the irradiation of a dye with light and the subsequent generation of reactive oxygen species (ROS) which are the effective phototoxic agents damaging virus targets by reacting with viral nucleic acids, lipids and proteins. Interestingly, a light-independent antiviral activity has also been found for some of these dyes. This review covers the compound classes employed in the PDI of viruses and their various areas of use. In the medical area, currently two fields stand out in which the PDI of viruses has found broader application: the purification of blood products and the treatment of human papilloma virus manifestations. However, the PDI of viruses has also found interest in such diverse areas as water and surface decontamination, and biosafety.

1. Introduction

1.1 Background and scope

With 2015 as the International Year of the Light, and in 2018 the declaration by the UNESCO that May 16th is the annual "International Day of Light", it is clear that the world is taking notice of light, photonics, lasers, renewable energy, biotheranostics, and more. Thus, it bears remembering that light is not only at the beginning of everything, but has the power to both nurture and kill. High energy radiation has in a sense brought 'us' to where we are in 'driving' evolution; however, this also presents a constant danger in terms of photomutations. Light is a crucial effector in many biological processes ranging from photosynthesis and vision, to phototropism and signaling, to name but a few. Light can also heal, as pointed out by Herodotus more than 2.5 millennia ago with his description of heliotherapy. Next to the healing effects of light alone, it can also be used as an activator of pro-drug–drug conversions in photomedicine. Classic examples are the photosensitized generation of reactive oxygen species (ROS) to combat malignant cells and tissue (photodynamic therapy, PDT)[1] and for the photodynamic inactivation (PDI) of microbes.[2]

The latter is of significant interest as antibiotic resistance,[3] the rise of new infections, the current security situation (with respect to bioterrorism, recurring military and disaster scenarios), as well as food safety[4] require the development of new strategies to combat bacterial and viral infections (Fig. 1).

As a result, recent years have seen a surge in studies on anti-microbial PDT,[2] with most studies focused on

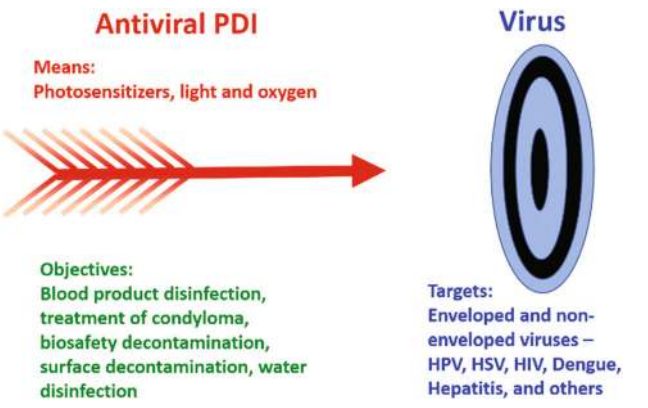

Fig. 1 Targets, means, and objectives of antiviral PDT.

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antibacterial[3,5] or antifungal PDT,[6] and these areas have been reviewed extensively. This field is also often referred to as PACT (photodynamic antimicrobial chemotherapy).[7] Here, we will focus exclusively on the area of antiviral applications.[2,7–9,10,11] Similar to antibiotic resistance, resistance to antiviral drugs is also a current cause of concern.[12] Thus, the photodynamic inactivation (PDI) of viruses is of interest as an alternative tool in antiviral treatments.[8,9,10]

The PDI of viruses can benefit from the same features relevant for PACT. The photodynamic mechanism rests on the light-induced formation of radicals, anions and, in general, ROS (*via* Type I and Type II mechanisms, see section 2) which damage the target cells or entities (*e.g.*, bacteria, viruses, or more recently, prions).[7–10,13] Though there are of course target structures for this damage (*e.g.*, membrane structures of tumor cells and bacteria, lipid structures or proteins of the viral envelope, or nucleic acids) this effect does not rely on the specific interaction with a receptor. This 'unspecificity' of photodynamic damage is one of its advantages with respect to PACT or PDI. Given the genetic flexibility of viruses (and bacteria) this untargeted mechanism of action is less prone to trigger the development of resistance in the target entity.[14] As resistance development is one of the main issues in fighting bacterial and viral infections, this makes PACT and PDI suitable to significantly contribute to the medical toolbox of fighting such infections and to overcome the increasing problem of antimicrobial resistance.

The photodynamic effect is only observed when light, a suitable photosensitizer (PS) and oxygen are present at the same time, hence photodynamic treatments are local treatments which usually limits their application to specific infection sites.[14] Thus, PDI of viruses has clinically been applied mainly to localized viral lesions (*e.g.*, herpes, warts – see later sections).[15,16] However, in recent years systemic effects of photodynamic treatment triggering immune responses have been identified.[17] This makes the PDI of viruses even more interesting as a complementary treatment option. In addition to treating viral lesions, PDI from the beginning offered potential in extracorporeal applications such as the disinfection of blood products (where it is now an accepted disinfection treatment – see later sections) or for laboratory viral safety measures.[18]

From a practical perspective one must note that there are now several PSs that have been approved for different medical treatments in patients, mostly for anticancer PDT.[19] The available evidence on preclinical and clinical safety of PSs facilitates their investigation for potential new fields of application such as the PDI of viruses. Recent years have also seen significant advances with respect to PS formulation development.[20–22] Some well-known PSs are highly lipophilic compounds, which hampers their administration and clinical application. By now, many new formulations have been investigated and authorized for medical use for these lipophilic PSs, which will also aid the development of antiviral treatments based on PSs. Still, while there is certainly potential in antiviral PDT, additional facts should be considered due to the complexity of this issue:

- The strong interdependence between light and the immune system.[23] Light alone can be used to treat viral infections.[15a,24] On the other hand some PSs may, in the absence of light, efficiently act as antivirals (see also further examples throughout).[25]
- The incidence of virus infection and cancer induction are sometimes connected, hence anticancer PDT may have antiviral PDI components as well. PDT is employed in (pre-)cancerous lesions induced by viruses, treating these cells with PDT

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can also reduce the virus load.[26–28] Indeed, PDT is often investigated for the treatment of pre-cancerous and cancerous lesions in the genital region.[27c,d,e,f] On the other hand, early antiviral PDI treatments of warts pointed at the risk of malignancy development in treated cells.[9]

• Photoinactivated viruses can still trigger an immune response, which may be unwanted but is also useful with respect to a competent immune response and vaccination.[18d,e,29]

• Some studies have reported a reactivation of viruses (*e.g.*, herpes simplex virus, HSV) by photodynamic treatments and viral inflammation as a side effect of PDT.[30] Treatment of cells with PSs has been shown to facilitate the infection with adenoviruses *via* a photochemical internalization mechanism.[31]

Another aspect of photodynamic action and viruses, outside of the scope of this review but currently attracting considerable interest, is the 'synergistic' combination of viruses/viral components and PDT. This entails the use of viral particles or components as targeting units (*e.g.*, peptides) or carrier systems (*e.g.*, virus capsids) in combination with PDT to treat tumors or bacteria.[32–34] PDT has also been used to augment the efficacy of oncolytic vaccinia viruses in metastatic tumors *in vivo*.[35] Analogously, PDT can be combined with the phage therapy of antibiotic resistant bacteria[36] and photochemical internalization (PCI)[37] has been combined with virus particles for virus transduction.[31]

In this review we intend to outline the state-of-the-art in the field of antiviral PDI by highlighting developments in medicinal chemistry, current viral targets and clinical applications, PS design and translational aspects. Even with this limitation the literature is already extensive with about 4000 publications to-date dealing with dyes and photoinactivation of viruses. Of these, over 1300 cover antiviral photodynamic effects and formed the starting point for our analysis.[38] The field is ripe for critical treatment in a monography, but that is outside of the scope of this contribution. Here, we focus on the various chemical classes of PSs, covering the medicinal chemistry thereof mainly for the past 10 years [2008–2018], and reviewing clinical and practical applications. We hope that a focus on the last decade will also serve to identify more clearly current trends in the PDI of viruses.

The literature basis for the current review were multiple searches in the CAS database with the respective search terms and combinations thereof, *e.g.*, 'photodynamic therapy', 'antiviral', 'photoinactivation', amended by specific searches for photoinactivation of viruses within the main PS compound classes (*vide infra*). Though this review focuses on photoactive compounds which exert their action *via* ROS (PSs), some compounds relying on a different phototoxic action mechanism – notably psoralens[39] – have also been included due to their clinical relevance. For the current review we chose an arrangement according to compound classes rather than virus targets, as the specific viruses studied in PDI investigations have often been chosen with respect to laboratory manageability (*i.e.*, model viruses) rather than direct medical relevance. Current developments with respect to medical applications of the PDI of viruses are included as well in the respective chemical sections, as the clinical application of PSs largely depends on their regulatory status, *i.e.*, clinical studies in PDI are mostly confined to specific PSs with an existing authorized indication such as antitumor PDT [*e.g.*, δ-aminolevulinic acid (ALA) and haematoporphyrin derivative (see later sections)].

Mathias O. Senge

Mathias O. Senge, Dipl.-Chem., M.A., Dr rer. nat., F.T.C.D., studied chemistry and biochemistry in Freiburg, Amherst, Marburg, and Lincoln. After a Ph.D. from the Philipps Universität Marburg (1989) and postdoctoral studies with K. M. Smith at UC Davis he received his habilitation in Organic Chemistry in 1996 at the Freie Universität Berlin. From 1996 on he was a Heisenberg fellow at the Freie Universität Berlin and UC Davis and held visiting professorships at Greifswald and Potsdam. In 2002 he was appointed Professor of Organic Chemistry at the Universität Potsdam and since 2005 holds the Chair of Organic Chemistry at Trinity College Dublin. He was the recipient of fellowships from the Studienstiftung des Deutschen Volkes, the Deutsche Forschungsgemeinschaft, and Science Foundation Ireland (Research Professor 2005–2009). His interests are synthetic organic chemistry, the (bio)chemistry of tetrapyrroles, photobiology and photomedicine, structural chemistry, and history of science.

1.2 Historical development

The historical development of the medicinal use of dyes[40] and PDT is well documented and has been the subject of several excellent treatises.[41] Thus, the story needs no retelling, although "what's past is prologue".[42] Yet, it must be emphasized – in the context of the many contemporary publications in this area selling this as a 'new' concept – that the discovery of phototherapy and PDI stands at the historical beginning of the entire PDT field, going back about 130 years.

Finsen's landmark treatment of *Lupus vulgaris*[43] is due to the photodynamic killing of *Mycobacterium tuberculosis*, probably *via* UV-A photosensitization of coproporphyrin III within the bacteria.[44] The effects of PS accumulation in humans were noted about the same time by Prime, who, during attempts to treat epilepsy, noted that oral administration of eosin resulted in severe erythema in sunlight-exposed skin.[41f,45–47] Raab and von Tappeiner's discovery in 1900, while attempting to develop antimalarials, that an external acridine dye upon light irradiation kills *Paramecium caudatum* presents the crucial experiment linking the photosensitizing effect of a dye and light.[48] The requirement for oxygen, the third component of the PDT triad, was proven shortly thereafter by Ledoux-

Lebards,[49] Straub,[46a] von Tappeiner and Jodlbauer.[50] These studies set the stage for all that followed in photodynamic therapy and even included what today we would call 'translational medicine', with Jesionek and von Tappeiner's treatment of a skin cancer with white light and topical eosin.[51] After that period, interest in PDT waned and it took more than half a century for studies on light-activated antiviral compounds[52] to begin in earnest, aided by the technological development of lasers.[53] The 1960s saw a flurry of reports on photo-induced antiviral effects of simple dyes such as methylene blue and other phenothiazine derivatives, acridine orange, among others. Viral study objects included, but were not limited to, arbovirus, SV40, poliovirus, encephalitis virus, phages, and HSV.[54] This period saw its ups and downs, *e.g.,* when a report on HSV inactivation[55a] resulted in controversy as it was shown that it putatively retained its oncogenicity after treatment with neutral red.[55] Clinical applications of PDI remained controversial for a time and over half of the aforementioned 1300 publications were published in the last decade indicating that, despite its long history, this is still a young and rapidly evolving field.

2. Mechanisms and targets for viral PDI

Past reviews[7a,9,40,56] and the more recent ones[3,8,10] have aptly described prior developments of the fields and the basic characteristics such as viral targets, photochemical mechanisms, and reactivity profiles. The fundamental mechanism of action of any PDT has three basic components irrespective of whether it is directed against tumor tissue, bacteria, viruses or other biological targets: a PS, light, and oxygen.[1,13,19a,b,57–59] The photochemical processes behind PDT start with the excitation of the PS with light of a suitable wavelength corresponding to the absorption spectrum of the PS (Fig. 2). Irradiation results in the formation of an excited singlet state of the PS, *e.g.*, the S_1 state. Upon irradiation with white light or sunlight, as employed in daylight PDT,[60] simultaneous excitation to the S_1 and higher singlet states occurs. Usually very rapid, faster than any other process, relaxation from these higher excited singlet states to the S_1 state occurs (Kasha's rule). From the S_1 state the molecule can either return to the ground state by emission of a photon (fluorescence) or by radiationless relaxation *via* internal conversion; or the molecule can, *via* spin inversion (intersystem crossing, ISC), form an excited triplet state, T_1. The return to the ground state is spin-forbidden which renders this T_1 state longer-lived. The molecule can now again return to the ground state *via* photon emission (phosphorescence) or radiationless decay *via* internal conversion. Most importantly, this T_1 state exists long enough to allow reactions with neighboring molecules, which are the ones relevant for PDT.

Two different follow-up reactions are possible: the first being that the molecule in the T_1 state can transfer an electron to other substrates (Type I photoreaction), *e.g.*, biomolecules, which gives rise to the formation of radicals – most prominently the superoxide anion radical (Fig. 3).[61,62] This can be converted to the much more cytotoxic hydrogen peroxide either enzymatically or through protonation. The superoxide anion radical can also reduce Fe^{3+} in cells to form Fe^{2+} and hydrogen peroxide, and in a second step Fe^{2+} can cleave hydrogen peroxide giving rise to highly reactive and cytotoxic hydroxyl radicals (Haber–Weiss/Fenton reaction). A possible direct charge transfer to oxygen plays only a minor role in this Type I photosensitization.[62]

Alternatively, the molecule can react in an energy transfer process with molecular oxygen whose ground state is a triplet state (Type II photoreaction) (Fig. 2). Thereby the PS returns to the ground state (S_1) while at the same time giving rise to the formation of singlet oxygen ($^1O_2$).[63] Notably, in Type II photoreactions the PS molecule can now be excited again, undergoing the same sequence and generating more $^1O_2$. Thus, both reactions give rise to the formation of ROS which are the actual toxic agents, and both are of course also involved in the PDI of viruses, as has been shown in multiple publications (see later sections).[8,10]

Many molecules can undergo this basic photochemistry,[13,57,64] though not all of these are suitable as PSs. Firstly, this depends on the probabilities (quantum yields) of the different processes, thus high quantum yields for singlet excitation, ISC, and energy transfer to (triplet) oxygen are needed for an effective Type II photoreaction. However, other parameters are

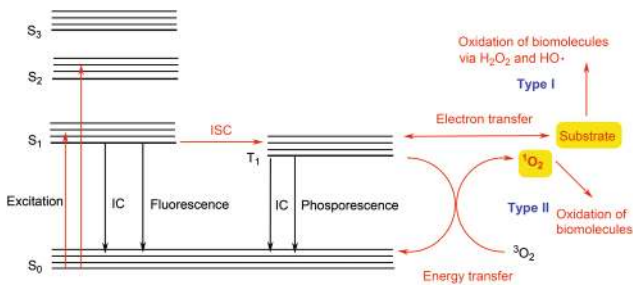


Fig. 2 Modified Jablonski diagram. Processes relevant for the formation of ROS and subsequent oxidative damage are depicted in red.

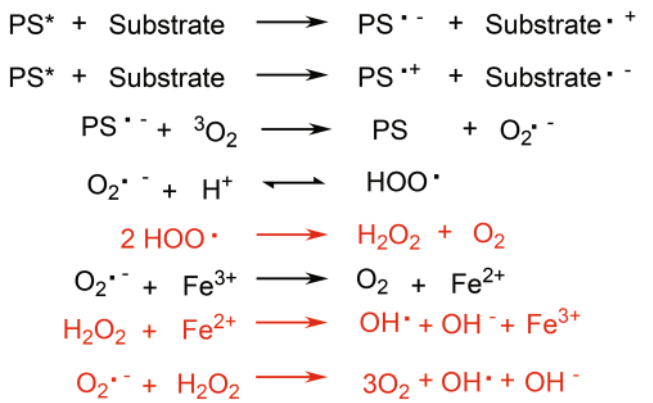


Fig. 3 Type I photoreactions. Reactions forming the main cytotoxic agents hydrogen peroxide and hydroxyl radicals, are depicted in red.

important as well; *e.g.*, effective generation of $^1O_2$ requires a suitable concentration of oxygen at the reaction site. The relative importance of Type I *vs.* Type II photoreactions therefore also depends on the local availability of oxygen.[10,65] In fact, continued irradiation under concurrent oxygen depletion due to PDT treatment of the tissue is probably one of the important factors relevant for the side effects observed in the PDT of tumors and intra-treatment detection of $^1O_2$ could contribute to enhanced PDT efficacy.[66–68] Hence, determining oxygen consumption and tissue oxygenation is an important issue in PDT[66] and considerable progress has been made recently with *in vitro* measurement of $^1O_2$ in living cells and tissue.[68,69] The question of oxygen consumption is directly connected to light dose and the light source. This has been extensively investigated for PDT[70] and has also been the topic of studies related to the PDI of microrganisms.[71–76]

Equally important is the localization of the PS. Effective PDT requires a localization of the dye near sensitive molecular targets in order to exert a significant effect. This is due to the short lifetime of $^1O_2$ in the biological environment. The decay has been shown to occur on a short μs time scale.[65c] The specific decay time depends on the localization of the PS, *e.g.*, it has been determined to be 0.4 ± 0.2 μs in the vicinity of membranes in living cells,[65a] or 1.2 ± 0.3 μs in blood vessels in a recent *in vivo* investigation,[65b] but much longer times have also been found.[65e] The intracellular diffusion distance is small relative to the cell diameter which means the effect of $^1O_2$ generated within a cell is spatially confined to its immediate surroundings. However, if generated near the cell membrane $^1O_2$ may be able to cross the membrane. The lifetime for radicals generated *via* Type I photoreactions is considerably longer, but they, too, exert their action through reaction with sensitive molecular targets such as proteins or the double bonds in unsaturated lipids. It is known in the PDT of tumors that amphiphilic/slightly lipophilic PSs are more effective than readily water-soluble ones. This is due to a preferred localization of the former in membrane structures of the cells where they can do more harm to the cells than in an aqueous environment.[77,78] On the other hand, PSs effective against (Gram-negative) bacteria are mostly (water-soluble) cationic compounds as these have a higher affinity to the bacterial membrane.[79]

Viruses have been estimated to be the most abundant and most diverse biological systems on earth.[80] Typically their size ranges from 0.02 to 0.3 μm, though very large viruses ranging up to 1 μm are known. Viruses depend on cells (plant, animal or bacterial cells) for their reproduction and are classified according to their genome and method of reproduction. They consist of a DNA or RNA (single or double stranded) core, an outer protein cover, and, in some virus classes, lipids. Diseases caused by viruses range from relatively harmless infections such as the common cold (caused by Corona viruses) or diarrhea and gastroenteritis (caused by, *e.g.*, Rota- and Adenoviruses) to serious diseases such as AIDS (caused by immunodeficiency viruses), Ebola (Ebola virus), SARS (SARS coronavirus) or, very recently, the Zika infections (Zika virus). In addition, virus infections are a well-known cause of certain forms of cancer [caused, for example, by HPV (Human Papilloma virus) or the Epstein-Barr virus].[26,27b,28a,b,c] Viral infections are also a serious problem in animal welfare and animal breeding.[81]

Based on the basic structure of viruses there are three principal molecular targets for viral PDI and for the reaction with the generated ROS: nucleic acids (DNA or RNA), virus proteins and, if present, viral lipids (Fig. 4).[8a,10] The latter present an additional target for ROS and hence, such viruses with lipids and/or a protein envelope, in general seem to be more sensitive to viral PDI than those without.[82–84] As commented on by Costa *et al.*,[10] there are no contemporary investigations specifically investigating the effect of PDI on viral lipids. This may in part be due to general difficulties related to lipid analysis.[85] On the other hand, there is indirect evidence for the deleterious effect of ROS on viral lipids and from investigations in anticancer PDT.[10,62,86]

In contrast, a significant body of information is available on the effect of ROS on viral nucleic acids and proteins as a result of PDI, and this has been reviewed extensively.[10,62,87] Photodamage to virus structures occurs *via* Type I and Type II photoreactions. Both mechanisms can be active at the same time, their relative importance being dependent on the PS structure, its concentration and the concentration of oxygen.[73,88,89] Thus, mechanistic investigations into the PDI of viruses are attempting to elucidate the contribution of the two mechanisms.[8,10] Experimentally this is done by adding specific quenchers for (oxygen) radical species (*e.g.*, glutathione, mannitol, dimethylurea or SOD)[88,90,91] or for $^1O_2$ (*e.g.*, sodium azide, *β*-carotene, histidine, or 1,3-diphenylisobenzofuran).[89,91,92] These quenching experiments unequivocally established the importance of both mechanisms in the PDI of viruses. Costa *et al.*,[10] in their concise evaluation of the literature involving quenching experiments, concluded that $^1O_2$ is the most relevant agent in the PDI of mammalian viruses, whereas radical species play a secondary role. For bacteriophages the results are more complex, though here also $^1O_2$ appears to play a major role. In some cases both processes seem to be concurrently active; *e.g.*, as was shown with the PDI of the T7 phage using glycosylated porphyrin PSs.[91] However,

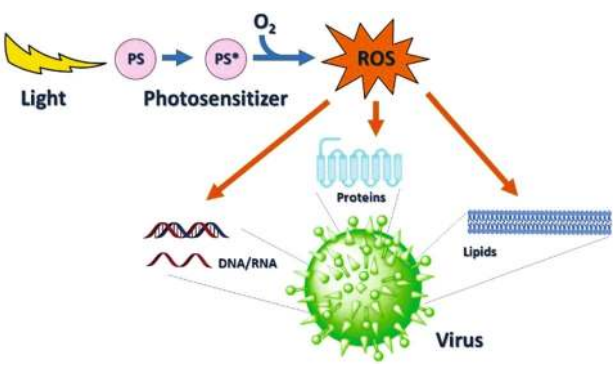


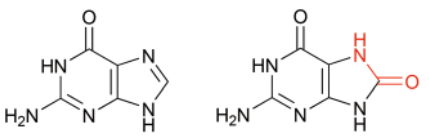
Fig. 4 The targets of PDI of viruses: nucleic acids, proteins, and lipids.

the situation is complicated by the fact that the relative importance of Type I and Type II photoreactions depends on the PS structure, and very rarely has the effect of different quenchers been investigated using constant PS and virus type.[73,88–91] One also has to keep in mind that there are additional oxygen-independent phototoxic mechanisms that can contribute to the virucidal activity in the PDI of viruses. This is especially prominent in the case of psoralens, which can generate $^1O_2$ but can also, upon UV-A activation effects, crosslink to pyrimidine bases.[18d,39,93]

DNA and RNA of viruses can be efficiently damaged by PDI. While PS binding or intercalation to the nucleic acids is not always needed for efficient photosensitization, it is known that cationic compounds, such as methylene blue, can cross the outer cover of viruses and intercalate into their DNA/RNA.[94] For cationic PSs, electrostatic interactions are supposed to allow direct PS-DNA/RNA interactions. In Type I photosensitized oxidation reactions with DNA and RNA bases, a key step is the addition of O_2 to short-lived carbon-centered radicals which originate from transformations of the primarily formed radical cations.[62] For Type II photosensitized oxidation reactions, [4 + 2]-, [2 + 2]-cycloadditions, and 'ene' reactions with $^1O_2$ dominate.[62] Such oxidative transformations destroy the DNA leading to fragmentation, single strand breaks, and cross-linking with proteins. Prevention of viral replication and reduction of infectivity following DNA damage by ROS has been shown.[8,10,95,96] Specifically, guanine moieties **1** are susceptible to oxidative damage yielding 8-oxo-7,8-dihydroguanine **2** as one of the main products (Type I photosensitized oxidation) (Fig. 5).[8,10,56,62]

Though viral DNA and RNA can be targeted by PDI, one has to remember that such direct DNA/RNA interference also principally bears the potential of mutagenicity.[11,97] Potential ramifications of this issue are exemplified by early clinical applications of PDI for the treatment of HPV infections, where in some patients the development of Bowen's disease after treatment was observed. Whether the PDI treatment was causative or not has been a subject of discussion in the literature.[9]

Some PSs (*e.g.*, ALA, PpIX, HPD, *vide infra*) have a high affinity to proteins and lipids. Such PSs are used to target the outer structures of the virus, *i.e.*, unsaturated lipids as well as envelope proteins.[10,62,86,98] Virus proteins typically undergo structural modifications such as protein cross-linking. Particularly, the photooxidative damage occurs at oxidation-sensitive amino acids such as tryptophan, methionine, cysteine, histidine and tyrosine. In addition, direct interaction of the PS with virus proteins may influence protein folding and thus affect virus function.[10,62]



1 Guanine **2** 8-Oxo-7,8-dihydroguanine

Fig. 5 Guanine **1** and its oxidation product **2**.

While the clinical interest in the PDI of viruses of course targets viruses relevant for human and animal health, bacteriophages (viruses replicating in bacteria) also play a notable role in the PDI of viruses. Bacteriophages are frequently used as models for evaluating potential PSs for antiviral phototherapy.[90,91b,92,98,99] Among other features, they are non-pathogenic to humans, more efficient, and easier to handle.[10] In addition, most bacteriophages are non-enveloped viruses, and as these are less susceptible to PDI, it can be considered that if a PS is active against them, it will also be active against enveloped viruses.[10]

As mentioned above, the PDI of viruses is characterized by a 'multi-target' mode of action – ROS being able to react with RNA/DNA, proteins and lipids alike. In some cases, *e.g.*, when treating HPV manifestations (see below), the antiviral effect is associated with purposefully killing the host cell (*i.e.*, eliminating the wart). However, there is also the possibility that PDI intervenes with specific stages of the viral life cycle.[8a] It is conceivable that viruses at different stages of the life cycle show different susceptibilities to PDI.[8a] This viral life cycle comprises the general stages of attachment of the virus to the host cell, penetration of the virus into the cell (fusion of cellular and viral membranes), uncoating of the viral RNA/DNA, replication of the viral genome, assembly of new virions from newly synthesized viral nucleic acids and proteins, and finally release of the new virions from the host cell.[100,101,102] Elucidating the specific effects of antiviral PDI on the different stages of the viral life cycle is a difficult task. However, a number of studies uncovering such specific PDI interactions has appeared (see also the discussion for the specific compound classes below), mostly related to RNA/DNA and protein interaction. Quite a number of these studies are related to the first step of the viral life cycle. PDI damage to viral proteins, for example, is sometimes associated with an inhibition of virus-cell fusion as some proteins play an important role in the attachment of viruses to the host cell surface. Lenard *et al.* could show that hypericin, as well as Rose Bengal, (for the specific discussion of compound classes see below) was able to inhibit virus fusion for the vesicular stomatitis virus (VSV), influenza virus, and Sendai virus (all enveloped viruses) by effecting cross-linking of viral proteins.[103] The damaging effect of PDI on viral proteins important for virus-cell fusion has also been demonstrated for specific phthalocyanines and HSV-1,[87] as well as for other PS and viruses.[98,104–108] Interestingly, for certain PS it could be shown that though proteins relevant for virus attachment are targeted, nevertheless the virus antigenicity is preserved, something desirable with respect to vaccination.[105–107] For example, for 1-iodo-naphthyl azide (see below Fig. 19) evidence was found that this compound selectively blocks virus-cell fusion at the pore formation and expansion step, while maintaining the antigenicity.[107] For HIV the inactivation of reverse transcriptase by a PS while maintaining the functional integrity of viral surface proteins has been demonstrated.[109] Inhibition of the fusion step has also been described by lipid membrane targeting.[110–112] As well, an activity of PDI in the later stages of the viral life cycle has been

elucidated in some publications.[10] For example, it was shown that PDI against HIV with ALA was not effective in the first infection phase.[113] Also, for a phthalocyanine a specific activity on the VSV viral RNA-RNA/polymerase complex has been reported.[10,114]

The *in vitro* protocols employed for evaluating the efficacy of PSs for antiviral PDI differ largely in the literature depending on the virus target. This makes comparisons of the activity of different PSs difficult, also, as often – instead of the target virus – model viruses are used.[8a,10,115] Moreover, all virus replication relies on host cell structures whereby those host cells also play an important role with respect to reliability and comparability of the assays.[8a,10,116,117] In general, the *in vitro* methods employed for determining antiviral PDI efficacy correspond to those used for non-light-activated compounds, amended by light activation protocols. General overviews on methods for determining antiviral efficacy are available in the literature.[116,118] A very comprehensive overview and compilation of the *in vitro* methods used for testing antivirals is given in the recent review by Rumlová and Ruml.[118] Information on *in vivo* models for assessing the antiviral efficacy is also given in reviews[15b,119] as well as in the discussion of the compound classes below.

3. Photosensitizers for viral PDI

3.1 Introduction

As previously described, the only (photo)chemical requirement for a compound to have potential photodynamic antiviral activity is its ability to generate ROS upon illumination. Thus, a wide range of chemically quite distinct classes of molecules have been evaluated for their use in PDI – ranging from plant extracts such as psoralen to early industrial dyes (recall the early use of eosin and acridine mentioned previously), other natural PSs, sensitizers used in other areas of PDT, synthetic compounds derived from medicinal chemistry QSAR projects, to fullerenes and carbon materials,[120] metals and oxides, complex synthetic $^1O_2$ generating and delivering molecular systems[121] as well as products from the materials sciences.

The example of psoralens illustrates an important additional aspect: apart from a photodynamic mechanism involving ROS (superoxide anion, hydroxyl radicals, $^1O_2$), psoralens also exert their phototoxic action on viruses *via* an oxygen-independent photochemical reaction.[39] Hence, compounds capable of such oxygen-independent inactivation of viruses have further contributed to the vast range of compounds employed for the photoinactivation of viruses.

In the subsequent text, the compound classes have been arranged roughly with respect to the status of their practical (medical/clinical) application in the PDI of viruses. Thus, the starting point entails compound classes for which there are up to now mostly *in vitro* investigations related to the PDI of viruses. These comprise compounds which have long been known as PSs, such as curcumins or hypericin, but also metal oxides and derivatives, as well as fullerenes and carbon nanomaterials. This is followed by, presumably, the most manifold class of PS, the tetrapyrroles – which for a long time have (and continue to) played a decisive role in the clinical PDT of tumors. Among these, specifically ALA and haematoporphyrin derivative (HPD) have progressed to clinical applications, mainly against different HPV manifestations.

Perhaps the area in which the PDI of viruses is most routinely used is the decontamination of blood products. Here, three main compounds and their derivatives are used: riboflavin, psoralen and methylene blue, which are reviewed consecutively. This is followed by an 'outlook' section on other PSs which have found interest in the PDI of viruses. Among them are compounds which were found to be potent antivirals and only at a closer look turned out to be PSs. With their different structures and approaches they provide further insight into the complexity of the field.

3.2 Curcumins

Curcumin (**3**), a polyphenolic compound isolated from turmeric, has been shown to exhibit a wide range of activities against various viruses[122] and has been used as a photocytotoxic agent.[123] However, due to poor bioavailability and significant reported metabolization, analogues to increase cellular uptake and absorption are desired for application in standard PDT.[124] De Clercq *et al.* designed bioconjugates with a view to improving the bioavailability of curcumin, and did so *via* functionalization of the phenolic groups (Fig. 6).[125] Two such compounds, **4a** and **4b**, with increased lipophilicity through peptide and fatty acid moieties, gave enhanced cellular uptake and these compounds also showed good results against VSV (**4a**) and both feline corona (FVC) and feline herpes viruses (FHV) (**4b**). A related compound **4c**, containing folic acid moieties, was found to be very active against HPV.

Other studies have also investigated the potential antiviral activity of curcumin against HPV associated cells.[126] Curcumin was cytotoxic against HeLa, SiHa and C33A cells, with a 57% and 63% reduction in viable cells on exposure to 60 μM of curcumin, to the former two cell lines, respectively. In addition to curcumin-induced apoptosis, selective inhibition of the expression of viral oncogenes E6 and E7 was observed, as well as downregulated *COX*-2 expression, a gene regulated by NF-κB.[126a] Finally, binding of AP-1, inherent to epithelial tissue-specific gene expression of HPV, was also selectively downregulated by curcumin.[126] The results provided very positive data for the use of curcumin in the treatment of HPV for novel cervical cancer treatments.

As it was observed to be a strong inhibitor of NF-κB signaling, it was postulated that curcumin may exhibit anti-viral activity against influenza A virus (IAV) propagation.[127] Indeed, treatment of MDCK cells with curcumin significantly reduced the viral titer at sub-cytotoxic doses (EC_{50} value of 0.47 μM), with less than 5% of mock-treated cells remaining. Moreover, the synthesis of viral proteins, such as haemagglutinin (HA) and neuraminidase was affected. The results indicated that the main target of curcumin is in the early stages of virus infection, most likely the attachment stage in the virus life-cycle.

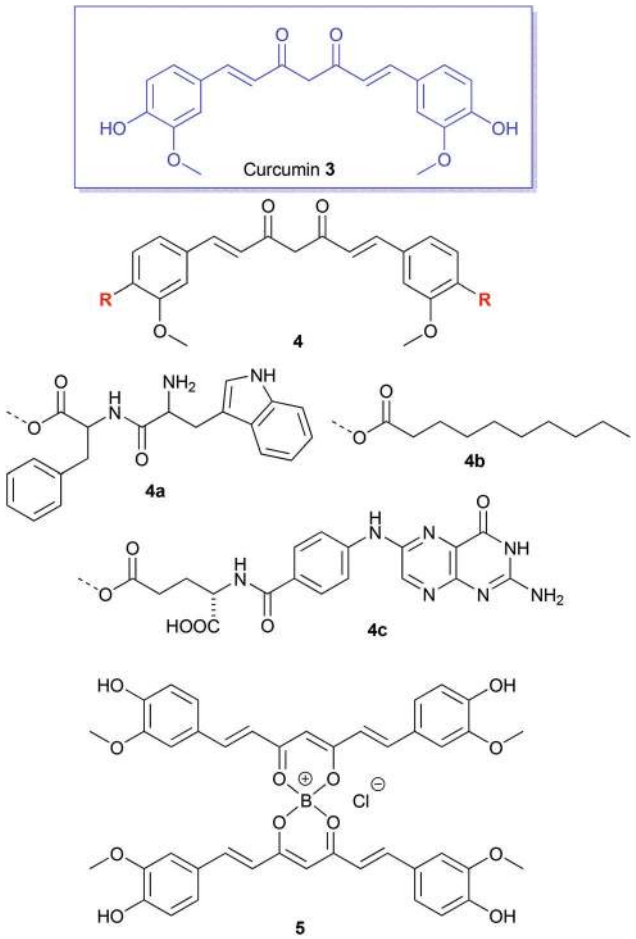


Fig. 6 Curcumin and selected bioconjugates.

This was confirmed *via* a plaque reduction assay. The activity was deemed to be a result of interference of curcumin with viral binding to sialic acid receptors at the cell surface. A HA inhibition assay confirmed that curcumin inhibits HA in IAV.

Curcumin has also been demonstrated to be effective against norovirus (NV) surrogates. For example, it was applied as a PS against murine norovirus 1 (MNV-1) in oysters, leading to significant inhibition as well as damage to viral nucleic acids.[128a] Photodynamic action of blue-light activated curcumin against MNV-1 was investigated *via* plaque assay to measure the viral load. It was shown that the viral morphology was altered after photodynamic activation, suggesting a change in the viral capsid protein structures. To that end, curcumin as a PS was deemed to be both an efficient and cost-effective method of inactivating food-borne NV. Another study assessed curcumin activity against NV surrogates FCV and MNV.[128b]

An inhibitory effect on human immunodeficiency virus type 1 (HIV-1) was observed upon treatment with curcumin, *via* suppression of the viral long terminal repeat-directed gene expression, stimulated by tumor necrosis factor α (TNF).[129] It was later demonstrated that curcumin exhibits anti-HIV-1 properties through diminishment of viral integrase and protease activities. HIV-1 integrase was inhibited by curcumin with an IC_{50} value of 40 μM, and results indicated interaction of curcumin with the integrase catalytic core. Energy minimization studies revealed that curcumin is able to fold back upon itself such that there is intramolecular stacking of the phenyl rings, bringing the hydroxyl moieties into close proximity within the active site.[130] Inhibition of HIV-1 and HIV-2 proteases, with respective IC_{50} values of 6 and 5.5 μM, was also demonstrated for curcumin boron complexes such as **5**.[131] Results suggested that the boron component forces an orthogonal orientation leading to simultaneous occupation of two binding sites in the protease active sites. Work by Bahraoui *et al.* aimed to develop molecules that would interfere with Tat transactivation of HIV-1 long terminal repeat.[132a] Derivatives included a hydrogenated curcumin, to prevent the previously described folding and therefore stacking of the phenyl rings, a diether to investigate hydroxyl moiety activity, and a diester to enhance lipophilicity. A 70–85% inhibition of Tat transactivation was observed in HeLa cells upon activation of *lacZ* expression. Curcumin was also shown to inhibit the histone acetyltransferase activity of transcriptional coactivator proteins p300 and CREB-binding protein *in vitro* (IC_{50} = 25 μM), thereby suppressing acetylation of the HIV-Tat protein.[132b]

Kutluay *et al.* investigated whether curcumin could act as an anti-herpetic compound by blocking immediate-early gene expression in HSV[133a] and reported a significant reduction in immediate-early gene expression, as well as a reduction in HSV-1 infectivity in cell culture assays. A later study investigated the potential of gallium- and copper-curcumin derivatives, reporting good antiviral effects on HSV-1 in Vero cell line culture assays.[133b] In addition, the infectivity of HSV-2 virions was decreased upon exposure to curcumin prior to infection of HeLa cells.[133c]

Aqueous extracts of *Curcuma longa* Linn. against hepatitis B virus (HBV) in HepG cells repressed secretion of HBV surface antigens.[134a] Production of HBV particles was also suppressed, along with the level of intracellular HBV RNAs, indicating inhibition of replication. The anti-HBV activity was attributed to an enhanced cellular accumulation of p53 *via* transactivation of p53 transcription as well as increased p53 stability. It was later demonstrated that curcumin inhibited a lipogenic transcription factor, sterol regulatory element binding protein-1, thereby suppressing hepatitis C virus (HCV) gene replication *via* the PI3K/Akt pathway.[134b] It was also observed that a combination of curcumin and interferon (IFN) resulted in a synergistic inhibitory effect on HCV gene replication, with treatment highly efficacious when compared to that of IFN alone. Antiviral activity was also reported against coxsackievirus B3 (Cox B3) *via* reduction of viral RNA expression, protein synthesis and virus titer.[134c] A protective effect was observed on cells against virus-induced apoptosis and cytopathic activity, with analysis of different pathways establishing that curcumin inhibited virus replication through dysregulation of the ubiquitin-proteasome system. Another report investigated the antiviral activity of curcumin on a Neuro2a cell line infected with Japanese encephalitis virus (JEV)[134d] wherein a modu-

lation of stress-related cellular protein levels, a decrease in cellular ROS levels and pro-apoptotic signaling molecules, as well as restoration of cellular membrane integrity was observed.

3.3 Perylenequinones

Perylenequinones comprise a range of natural products such as hypericin, hypocrellin and derivatives which exhibit distinct (photo)pharmacological activity.[135]

3.3.1 Hypericin. Hypericin (4,5,7,4′,5′,7′-hexahydroxy-2,2′-dimethylnaphthodianthrone, **6**) is an anthraquinone derivative and one of the main active compounds in St John's wort (*Hypericum perforatum* L.) (Fig. 7).[136–138] St John's wort is a traditional herbal medicine used mainly for the treatment of mild-to-moderate depression but also other indications such as bacterial infections and respiratory conditions,[136,137,139] and is commercially available as standardized extracts, tea leaves, as well as oil infusions for topical use.[137] With the exclusion of hypericin, St John's wort extracts contain a multitude of other components which also contribute to its pharmacodynamic effects, *e.g.*, hyperforin (**7**), which plays an important role with respect to the drug-drug interactions observed with St John's wort.[137,140]

The photosensitizing action of hypericin has long been established;[138] light-sensitivity is one of the well-known side effects of hypericin-based medicinal products and goes back to ancient times.[137] There are numerous studies, including clinical trials, on the photodynamic action of hypericin and its derivatives against tumors; and also to a lesser extent against bacteria.[136,141,142] Recent research has additionally focused on the *light-independent* pharmacodynamic effects of hypericin derivatives.[142–144] Pronounced toxicity of hypericin against tumor cells in the absence of light has been reported and possible mechanisms are discussed in the literature.[143,144]

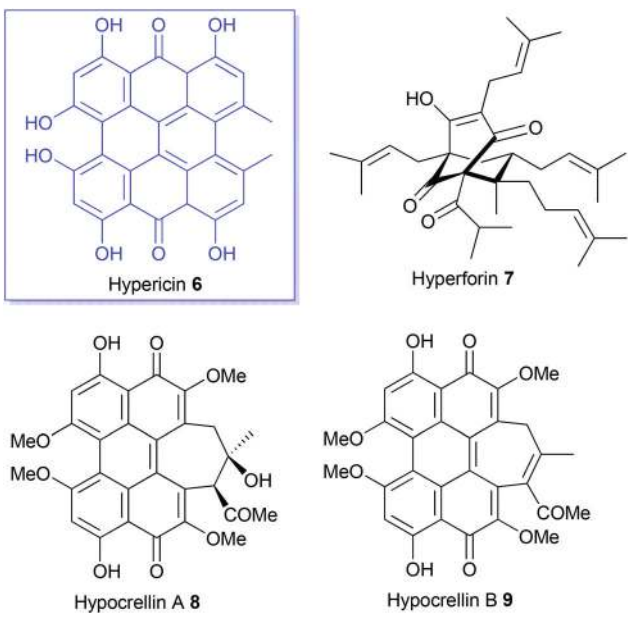


Fig. 7 Hypericin **6** and hyperforin **7**, and hypocrellins.

Hypericin has also been investigated for its antiviral properties.[145] A notable review by Kubin *et al.* gives an overview on the different viruses and testing conditions employed for investigating these antiviral properties, both under light irradiation and light-independent conditions.[146] Hypericin has been found to inhibit viral infectivity for a number of different viruses (*e.g.*, HSV, HIV, IAV and VSV); for several viruses a light-independent antiviral activity has been observed.[146] Earlier investigations looked at the utility of hypericin for the inactivation of infectious viruses in red blood cells.[147]

Based on promising *in vitro* results two phase I clinical trials were performed in 1999 and 2001, one in HIV-infected patients and the other in patients with HCV.[148,149] The phase I dose escalation study in patients with chronic HCV infection was set to determine the safety and (light-independent) antiviral activity of hypericin. Pharmacokinetics showed a long elimination half-life for the two doses (0.05 and 0.1 mg kg^{-1}) studied, with mean values of 36.1 and 33.8 h, respectively. The main side effect was phototoxicity, no anti-hepatitis C activity was detected.[149] In the other phase I dose escalation study (0.25 or 0.5 mg kg^{-1}) of HIV infected patients, cutaneous phototoxicity was so severe that dose escalation could not be completed, and no anti-retroviral activity could be observed.[148]

The antiviral phototoxicity of hypericin and its derivatives has been shown to depend on (light and) oxygen.[150] Hypericin is able to generate $^1O_2$ and other ROS,[136,145,146] underlining its role as a classical PS. However, it has also been discussed whether a release of protons from hypericin upon irradiation, leading to a photogenerated pH drop, contributes to its antiviral properties, as enveloped viruses often depend on specific pH conditions during their life cycle.[151] On the other hand, the PDT effect of hypericin is attenuated by endogenous proteins such as gluthathione-*S*-transferase.[152]

3.3.2 Hypocrellins and related compounds. Hypocrellins such as hypocrellin A (**8**) and B (**9**), are structurally related to hypericin and were isolated from the Chinese medicinal fungus *Hypocrella bambuase*, possessing both photodynamic anticancer and antiviral activities.[136*b*,153] Similar to hypericin, efforts are under way to advance chemical functionalization and nanoformulation methods,[154] and to improve possible biotechnological production of such compounds.[155]

Given the structural variability of hypericin and related compounds, and the variety of these compounds occurring in nature, there is an ongoing search for photoactive compounds based on this skeleton,[135,136,156,157] including clinical investigations with new promising structures.[158]

3.4 Metal oxides and other inorganic materials

The inorganic Material Sciences have not stood back in the fight against viruses. Recent developments and potential applications of metal derivatives, notably oxides, are increasingly described in reviews.[8,159] Potent virucidal activity has been reported for numerous metal complexes and metal oxides. An early study by Smith *et al.* examined a series of platinum pyridine complexes and their activities against various viruses.[160] The tridentate 2,2′-dihydroxyazobenzene and 2-salicylidenea-

minophenol derivatives were shown to exhibit virucidal activity against enveloped viruses; equine infectious anemia virus (EIAV), HIV-1 and HSV-1. All experiments were carried out using ordinary laboratory light with an irradiation time of 30 min, and viruses were shown to be completely inactivated at concentrations as low as 1 μg mL^{-1} in solution.

Park *et al.* investigated the mechanism and efficiency of MNV-1 inactivation using TiO_2 on solidified agar matrix.[161] UV-C light was found to be the most effective in reducing viral titers, with negligible levels remaining after a 5 min treatment. It was observed that the hydroxyl radicals produced upon light irradiation were responsible for MNV-1 inactivation, quantified using *p*-chlorobenzoic acid as a probe. The purpose of the study was to simulate blueberries and establish an effective method for reducing the risk of HNV infection in fresh produce, which was successfully demonstrated using the solidified agar matrix. TiO_2-mediated photocatalytic decomposition,[162] in principle, offers a practical means for antimicrobial treatment in conjunction with environmental remediation of pollutants,[163] possibly using ultrasound activation.[164] An even simpler approach to improve the photodynamic effect of many PSs is the addition of 'inorganic salts', *e.g.*, azides and iodides. This approach, widely used by Hamblin's group in antibacterial studies,[165] who "discovered that aPDI can be potentiated (up to 6 logs of extra killing)",[165a] offers a very straightforward and simple (in terms of regulatory affairs) means for PS improvement.

The virucidal activity of up-conversion nanoparticles (UCNPs) was demonstrated by Chu *et al.*, with significant results obtained both in suspension and a murine model.[166] This UCNP-based PDI strategy was envisaged to overcome common problems with current PDT approaches, such as PS hydrophobicity, poor target specificity and limited tissue penetration. Near infrared (NIR)-to-visible UCNPs consisting of $NaYF_4$ nanocrystals were synthesized and co-doped with Yb^{3+} and Er^{3+} ions. The UCNPs were then coated with a layer of high molecular weight polyethyleneimine (PEI) to "solubilize" the non-polar UCNP core, and (phthalocyaninato)zinc(II) (ZnPc, the PS) molecules were physically adsorbed to the surface. On irradiation at 980 nm, the material emitted visible light, absorbed by the PS which converted nearby molecular O_2 to ROS, resulting in viral inactivation. The Dengue virus serotype 2 (DENV2, New Guinea C strain) was chosen and the IC_{50} was determined to be between 4.4 and 44 μg mL^{-1} in suspension. The *in vivo* study gave promising results, with 100% of the suckling mice surviving to the final day of observation upon treatment with 440 μg mL^{-1} of ZnPc-UCNPs. To investigate target specificity, the ZnPc-UCNPs were conjugated with an antibody specific for the DENV2 envelope protein. The immunofluorescence assay revealed specific localization onto virus-infected cells only. The study also investigated virucidal activity against the non-enveloped virus, AdV5, and achieved significant reduction in viral titer.

Dragnea *et al.* described the incorporation of CdSe/ZnS semi-conductor quantum dots (QDs) into viral particles.[34d,e] The QDs were assembled inside the capsids of brome mosaic virus, a simple icosahedral virus. The result was a virus-like particle of similar size to the native virus, using easily manipulated PEG coatings to facilitate future industrial applications.

3.5 Fullerenes and carbon materials

Fullerenes and other carbon materials such as carbon nanotubes or, more recently, graphene have been envisioned for many biological and medical applications (Fig. 8).[99,100] The antiviral potential of Buckminster's fullerene (C_{60}, **10**) and its derivatives was shown by Friedman *et al.* by inhibiting HIV-1 protease – in the absence of light.[167] A few years later the photodynamic antiviral activity of C_{60} was demonstrated.[83] PDT with fullerenes has been reviewed by a number of authors[168] and their possible role in photodynamic viral inactivation has been addressed as well.[8]

Fullerenes and their derivatives have been tested against a number of viruses such as Semliki Forest virus (SFV), VSV, HSV-1, HIV-1, mosquito iridovirus (MIV) and IAV, and the phage MS2.[83,90] With respect to their photophysical features, fullerenes are characterized by the formation of long lived triplet states, the ability to generate $^1O_2$ and other ROS, as well as a high resistance to photo-degradation.[8a,168b,c,169] These properties render them suitable as PSs. Interestingly, fullerenes exhibit Type I as well as Type II photochemical reactions which

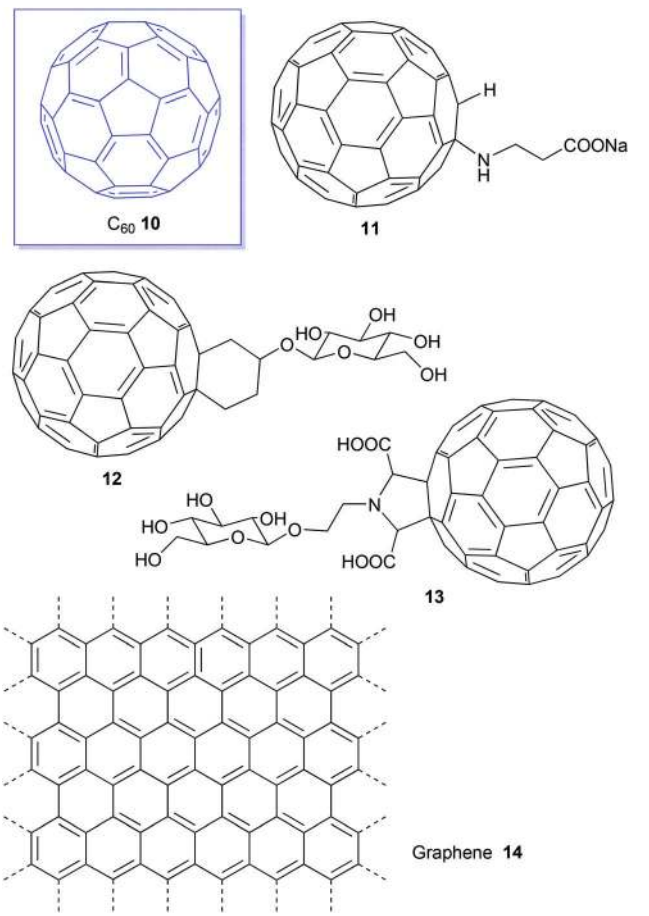


Fig. 8 Carbon materials used as PSs.

is in contrast to, for *e.g.*, tetrapyrrole PSs which in general predominantly undergo Type II photochemistry.[57,168c,170] However, due to their hydrophobic nature and thus low solubility in polar solvents, fullerenes pose problems for biological and medical applications, and significant work has been invested in their functionalization to find suitable formulations.[99c] In some cases, C_{60} has been used in the form of aqueous suspensions[83,171] or it has been formulated with polymers such as mPEG or polyvinylpyrrolidone (PVP).[152] Alternatively, C_{60} can be functionalized with moieties enhancing solubility in polar solvents,[172–174] *e.g.*, as polyhydroxylated[92,175] or cationic derivatives.[176,177] In particular, cationic derivatives such as fullerenes with three *N*-methyl pyrrolidinium groups exhibited high antiviral activity under irradiation.[177]

A study by Tanimoto *et al.* demonstrated that HIV-1 protease photo-degradation by compound **11** (Fig. 8) could be significantly enhanced by preparing the glyco-substituted derivative **12**, which still showed low solubility. Thus, preparation of **13** with two additional carboxyl groups became necessary to increase the solubility in aqueous media.[178] This compound effectively degraded HIV-1 protease under photoirradiation and was able to inhibit HIV-1 replication in living cells.

Granted, the low aqueous solubility of fullerenes can also be used as an advantage to exploit them as photoactive materials which can be easily removed from biological media after use. For example, aggregates of C_{60} have been used against HSV-1,[179a] and both C_{60} and C_{70} have been loaded onto silica.[179b,180] Recently, C_{70} and silver have been loaded onto polymer NPs in order to obtain a dual functionality against viruses and bacteria. The respective nanocomposites were successfully tested in the synergistic inactivation of a model virus (bacteriophage PR772) and *Escherichia coli*.[181a] In this context it should be noted that fullerenes can also be used as scaffolds for the design of carrier systems for other PSs, *e.g.*, porphyrins.[181b] Such fullerene based carrier systems for PS have been tested *in vitro* for their PDT activity against tumor cells.[181b,c,d]

There have also been a few reports on the use of graphene materials. Hu *et al.* used a graphene oxide-aptamer conjugate to target the phage MS2 as a model virus,[182] while Akhavan *et al.* showed that photoirradiation of graphene-tungsten oxide composites resulted in protein destruction and RNA efflux in MS2.[183] It should be mentioned that graphene materials bear potential not only for PDI of viruses but also for deactivation of viruses *via* alternative mechanisms, *e.g.*, *via* selective binding. Deokar *et al.* recently synthesized sulfonated magnetic NPs functionalized with graphene oxide. This nano-construct exhibited a high antiviral activity against HSV-1 *via* photothermal destruction.[184] Likewise, polyglycerol sulfate-functionalized graphene sheets were shown to selectively bind and thus inhibit the African swine fever virus, one of the most dangerous pig diseases and critical for livestock breeding.[185]

Similar to other compounds used for PDI of viruses, it should be kept in mind that such compounds may have antiviral properties in the absence of light also (*e.g.*, fullerenes[167,175]). Therefore, substantial control experiments are necessary to elucidate the mechanism of antiviral activity as well as the oxygen dependence of virus photoinactivation, and the presence of oxidized species following virus inactivation has been investigated in many studies[83,172,176a,182,183] and is also discussed in respective reviews.[168]

3.6 Porphyrins and porphyrinoids

Porphyrins and porphyrinoids (compounds with alterations to the porphyrin skeleton) are perhaps the most prominent class of PSs since the famous experiment of Meyer-Betz in 1913, when he injected himself with a derivative of haematoporphyrin.[46b] Since then virtually any class of porphyrinoids has been tested for their photodynamic properties. Apart from porphyrins **15**, this also includes chlorins **16**, bacteriochlorins **17**, corroles **18**, phthalocyanines **19** (Fig. 9) and others.[13,19a,64,186–191] Many of these have also been investigated for the PDI of viruses. Porphyrinoids also dominate the PSs authorized for clinical use in PDT, such as ALA (as the precursor of protoporphyrin IX, *vide infra*),[19a,187,192] haematoporphyrin derivative (HPD) and its congener Porfimer sodium,[19a,187] Temoporfin,[19a,187,193] or Verteporfin (the latter being mainly applied in the photodynamic treatment of age-related macular degeneration).[19a,187,194]

3.6.1 Porphyrins. The PDI of viruses with porphyrin PSs has been reviewed as part of general reviews[8a,9,10] as well as in specific reviews dealing with this compound class.[195–198] Recent publications on synthetic porphyrins, as opposed to those derived or related to natural dyes, are mainly concerned with *in vitro* investigations on the PDI of viruses, whereas clinical studies have centered on PSs such as ALA or HPD.[16c,26b,27b,199] This reflects the accumulated medical knowledge and regulatory status of the latter which have now been used in clinical practice for decades.[13,19a,167]

3.6.1.1 Synthetic porphyrins. Recent work on the PDI of viruses with porphyrins has focused on cationic porphyrin derivatives, specifically *N*-methylpyridyl-substituted

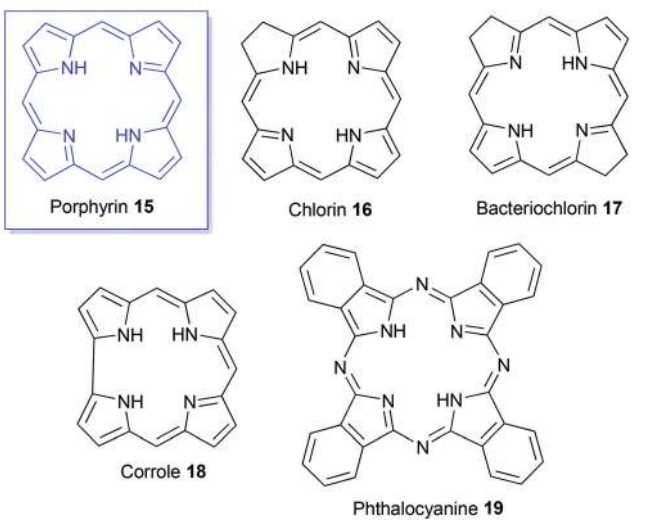


Fig. 9 Main classes of porphyrinoids employed in the PDI of viruses.

compounds.[75,89,98,200–208] Cationic porphyrins are well known to be effective in the PDI of bacteria as well as viruses.[5,15,209–212]

Costa *et al.* investigated the structure-activity relationship in a series of cationic porphyrins carrying two to four charges in the PDI of the T4-like sewage phage, a non-enveloped double stranded DNA virus.[202a] With the tri- and tetracationic porphyrins it was possible to reduce the phage to the limits of detection; however, the mono- and dicationic species did not yield a significant reduction of phage viability.[202a] The highest activity was observed for 5,10,15,20-tetrakis(*N*-methylpyridinium-4-yl) porphyrin tetraiodide (**20**) and 5-(pentafluorophenyl)-10,15,20-tris(*N*-methylpyridinium-4-yl)porphyrin triiodide (**21**) (Fig. 10). Interestingly, in the series of tricationic porphyrins (**21** and **22**), that with the polar carboxylic acid-substituent was the least active, which may point to a higher activity of compounds with an amphiphilic substitution pattern, *i.e.*, combining polar cationic and unipolar substituents such as pentafluorophenyl. High antiviral activities for tri- and tetracationic porphyrins were also observed in other investigations.[200,201,212a] Tomé *et al.* have compared a mono-galactosylated tricationic porphyrin to the corresponding neutral compound,[200] in an extension of earlier work.[213] They found both compounds to be active in the PDI of HSV-1; however, the viral inhibition was more dependent on photoactivation for the neutral rather than for the cationic compound, *i.e.*, the cationic compound exhibited virus inhibition also in the absence of light.[200]

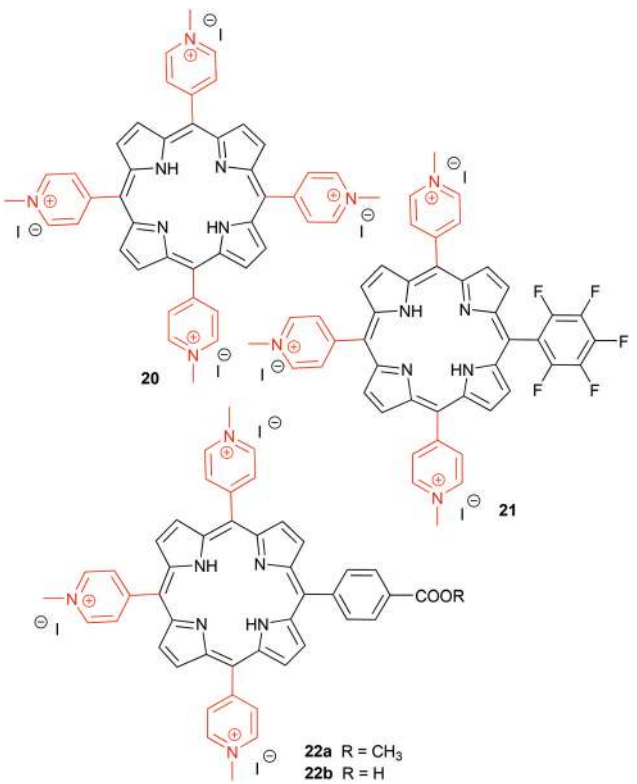


Fig. 10 Selection of structures used in the QSAR study on the antiviral activity of *N*-methylpyridyl-substituted porphyrins by Costa *et al.*[202a]

Costa *et al.* have subsequently used compounds **20** and **21** in more detail in several related publications,[75,89,203,204,205] using the T4-like sewage phage as a model, as well as other phages. PDI of phage T4 with these porphyrins was shown to be dependent on the light source, fluence rate and total light dose with phage activation being more effective at lower fluence rates.[75] In a comparative investigation of PDI with 5-(pentafluorophenyl)-10,15,20-tris(*N*-methylpyridinium-4-yl) porphyrin triiodide (**21**) in a series of DNA (T4-like sewage phage, phage of *Aeromonas salmonicida*, phage of *Vibrio anguillarum*, and the phage of *Pseudomonas aeruginosa*) and RNA (Qβ, phage MS2, phage LAIST_PG002) phages, compound **21** was able to inactivate all phages. However, the inactivation of the RNA phages required less time and lower PS concentrations than for DNA phages.[204]

The authors also investigated the mechanism of viral photoinactivation for the DNA-phage T4 and the RNA-phage Qβ.[89] The protective effect of $^1O_2$ quenchers (sodium azide and L-histidine) and of free radical scavengers (D-mannitol and L-cysteine) against PDI with the aforementioned cationic porphyrins was assessed in both phages. The $^1O_2$ quenchers exerted a significant protective effect against PDI, thereby confirming a Type II photodynamic mechanism for the photoinactivation of the phages with these PSs. The protective effect was lower for the Qβ phage reflecting the higher sensitivity of RNA phages to PDI.[89] Majiya *et al.* in a mechanistic approach investigated the PDI of the phage MS2 with 5,10,15,20-tetrakis (*N*-methylpyridinium-4-yl)porphyrin tetra-*p*-toluenesulfonate and identified the A-protein of the virus capsid as the primary target of photodynamic damage.[98] That direct binding to viral DNA is not a prerequisite for efficient PDI was also determined in an investigation with the T7 phage using (*N*-methylpyridinium-4-yl)-substituted PS.[201] In this case, free porphyrin was found to be more effective as a PS than DNA-bound porphyrin.[181]

Resistance formation has also been discussed as an issue for the photodynamic inactivation of bacteria and viruses.[203,214] In a series of ten consecutive cycles of PDI against the T4-like bacteriophage with PS **21** no resistance formation was observed. This is in line with the 'multi-target' mode of action of PSs which lowers the probability of resistance formation.[203]

Vargas *et al.* tested the PDI of HIV-1 with a number of different metal complexes of 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin.[215] The HIV glycoprotein gp120 is known to interact with anionic porphyrins.[216] The investigation identified distinct differences in the antiviral activity of metal complexes. Whereas there was no antiviral activity for the Cu(II), Ni(II), and Co(II) complexes, the PSs with Type I activity (Fe(III), Mn(II)) as well as those with Type II activity (Pd(II), Zn(II)), were effective in the PDI of HIV.[215] Similarly, a comparative study of cationic and anionic PSs with bovine herpes virus (BoHV) type-1 indicated a higher activity for zinc(II) complexes.[217] In a concurrent approach, 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin has been loaded onto fullerene. This nanoparticle PS was effective in the PDI of HSV-1, the PS loaded on fullerene being more efficient than the free PS.[218]

More recently, some publications described antiviral materials.[206,208,219] In this respect [5-(4-methoxycarbonylphenyl)-10,15,20-triphenylporphyrinato]platinum(II) was attached to nanoporous alumina membranes capable of inactivating VSV.[219] Carpenter *et al.* have bound a tricationic (*N*-methylpyridinium-4-yl)-substituted porphyrin to cellulose paper on which PDI of influenza A, DENV and human AdV5 could be shown.[206] In a similar approach from the same team, this porphyrin was embedded in polyacrylonitrile nanofibers and the material was photodynamically active against human AdV5 and VSV. The latter material gave a higher level of photodynamic inactivation compared to the cellulose-based materials, which was attributed to higher PS loading and a greater surface area in the case of the polyacrylonitrile nanofibers.[208] Peddinti *et al.* reported bulk thermoplastic elastomer films containing ~1 wt% (5,10,15,20-tetrakis(*N*-methylpyridinium-4-yl)porphyrinato)zinc(II) that were active against VSV (enveloped) and human AdV5 (non-enveloped).[220]

3.6.1.2 Naturally derived porphyrins – ALA and haematoporphyrin derivatives. More recent studies using naturally derived PSs employed ALA (**23**) and PpIX (**24**) (Fig. 11).[8a,221,222] The use of ALA and its derivatives for the PDI of viruses has been covered by a number of general reviews that deal with PACT as well as other off-label applications for this compound.[16c,27,199,222,223] The potential of ALA/PpIX for the PDI of viruses is long established[224–229] and the work with this PS (precursor) benefits from the acquired clinical knowledge and also its regulatory status, as the compound is approved in the EU and the USA for treatment of actinic keratosis.[230] These preconditions facilitate the use of ALA in other medical fields such as the PDI of viruses. Hence, most publications deal with related clinical applications of ALA and its derivatives.[16c,27,222,223a]

Among these, due to the localized PDT treatment, the most common application is the treatment of different manifestations of HPV,[24a,224,231–234] *e.g.*, acral[233,235–242] and facial[243,244,245] warts or warts in the genital region (*Condylomata acuminata*).[219,246–257] In addition, antiviral PDT has been of interest in the treatment of recurrent respiratory papillomatosis.[248] Apart from treatment, ALA can of course also be employed in the fluorescence diagnosis of HPV infections.[246] For the most part, ALA has been employed, however methyl aminolevulinate (MAL) and hexaaminolevulinate (HAL) have been applied successfully as well.[235,237] In the majority of these studies the efficiency of PDT for the treatment of viral warts has been demonstrated,[233,235–238] though there are also studies in which only a moderate efficiency of PDT was observed.[239]

In a study by Fuchs *et al.* light alone (water-filtered infrared A) achieved a considerable effect.[241] Successful treatment of warts with laser alone has also been reported by other authors.[24a,d] In a large randomized clinical trial (ALA-PDT as adjuvant treatment to CO_2 laser) of *Condylomata accuminata*, the ALA-PDT treatment did not show additional benefits.[256] A randomized trial with 80 patients comparing cryotherapy plus ALA-PDT and cryotherapy alone for the treatment of multiple *Condylomata acuminata* found the combination of cryotherapy and ALA-PDT to be more effective than cryotherapy alone.[258] The evaluation of the ALA-PDT treatments of 531 patients showed an increase of the clearance rate with the number of PDT cycles. In addition, the clearance was higher for small lesions (ϕ < 5mm) than for larger lesions, and depended on the site of the lesion.[259] In a comparative investigation of different methods to treat *Condylomata acuminata* with 361 patients the authors concluded that the treatment should be chosen according to the diameter of the lesion to be treated. For lesions with a diameter <0.5 cm ALA PDT is proposed, for lesions >2.0–4.0 cm cryotherapy or CO_2 laser treatment followed by ALA treatment is recommended, and for lesions with a diameter 0.5–2.0 cm a combination of ALA-PDT and cryotherapy is suggested.[250]

Though more feasible for smaller lesions, the treatment of large *Condylomata acuminata* (Buschke–Löwenstein tumor) has been reported, too.[260] In the cells ALA is transformed to PpIX, which is the active PS. The pharmacokinetics of PpIX after ALA administration has been followed in patients with urethral *Condylomata acuminata*, allowing determination of the optimal concentration and residence time for the ALA solution.[251] Very recently it has been shown that the monitoring of HPV genotypes and viral loads in PDT treatment of *Condylomata acuminata* can help to optimize PDT treatment and can be indicative of PDT treatment efficacy.[248c] Likewise, the connection between ALA-PDT of *Condylomata acuminata* and the level of regulatory T cells, serum TGF-β1, and lymphotactin has been investigated, showing that low levels of serum TGF-β1 and lymphotactin played an important role in the occurrence and development of *Condylomata acuminata*.[261] ALA, MAL or HAL are usually applied topically,[235,237,239–241,243–245] though an intralesional injection has been successfully tested as well.[236] The use of a high-pressure needle-free injection for this treatment has also been reported.[262] Apart from *Condylomata acuminata*, ALA-PDT has successfully been used to treat the HPV-related Bowenoid papulosis.[263]

The most prominent side effect of the treatment of warts with PDT is pain;[232,235,238,239,245,253] other reported side effects include erythema,[238,239,245] exfoliation, and postinflammatory

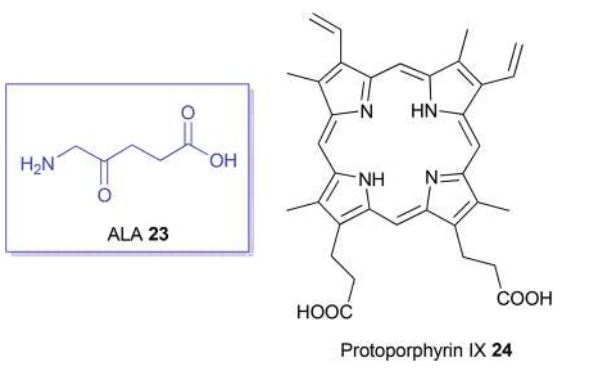


Fig. 11 ALA and protoporphyrin IX.

hyperpigmentation.[245] Ulceration and photoonycholysis were observed in the case of intralesional injection of ALA.[236] In addition, bacterial infections after ALA-PDT of *Condylomata acuminata* have been reported; these can be avoided by prophylactic topical antibiotics.[264]

PDI has also been used in the treatment of HPV in immunosuppressed patients.[244,265] Due to the reduced immune status HPV can more easily spread, on the other hand a control of warts is specifically important in this patient group as certain types of HPV can be a source of neoplastic lesions.[266] Xu *et al.* compared the efficacy between CO_2-laser treatment alone and the combination of CO_2-laser and PDT for the treatment of *Condylomata acuminata* finding the highest efficiency in the combination of both,[247] as also observed by Šmucler *et al.* for the treatment of *Verruca vulgares.*[24a]

An important field of application for ALA and its derivatives MAL and HAL is also the treatment of HPV-induced (pre-)cancerous lesions, or of high-risk HPV infections.[27,267–272] In a recent study by Chang *et al.*, patients with persistent high-risk HPV infection were treated with topical ALA-PDT, with remission rates of 64% observed.[269b] While in this case the primary targets are the (pre-)cancerous lesions, there is also an effect on the virus load by the PDT treatment.[27b,270,271] Apart from the treatment of HPV there have also been investigations on the PDI of other viruses such as HSV.[15a,b,113]

Very recently, it was shown that heme, Co- and Sn-PpIX can inactivate Zika, Chikungunya and other arboviruses by targeting the viral envelope. Interestingly, all three porphyrins showed a light-independent antiviral activity; however, the antiviral activity of Sn-PpIX could be enhanced with light irradiation.[273] The same three porphyrins also showed a light-independent antiviral activity against yellow fever and the Dengue virus.[274]

Compared to ALA and its derivatives, recent years have seen fewer publications related to the PDI of viruses using haematoporphyrin derivatives.[26b,275–278] Yin *et al.* investigated the PDI of bovine and human immunodeficiency virus with haematoporphyrin monomethyl ether (HMME). HMME successfully inhibited HIV in *in vitro* experiments. The antiviral effect could be quenched by both the $^1O_2$ quencher sodium azide as well as by the hydroxyl radical scavenger D-mannitol.[276] Like ALA, HPD has also been applied to cervical intraepithelial neoplasia.[26b,277] In a nanoparticle-based approach targeted to develop *ex vivo* reusable antiviral agents Banerjee *et al.* have connected PpIX to multi-walled carbon nanotubes and showed that this conjugate was capable of reducing the infectivity of influenza A virus in mammalian cells.[96]

3.6.2 Chlorins. Chlorins (**15**) (and bacteriochlorins) have long been established as PSs for PDT,[187,279,280] specifically because of their stronger absorption at higher wavelengths which renders them more effective PSs as a result of deeper tissue penetration.[281,282] Apart from synthetic chlorin systems,[281] chlorins derived from natural sources [modified chlorophyll derivatives such as chlorin e_6 (3^1,3-didehydrorhodochIorin 15-acetic acid), **25** or phytochlorin, **26**]

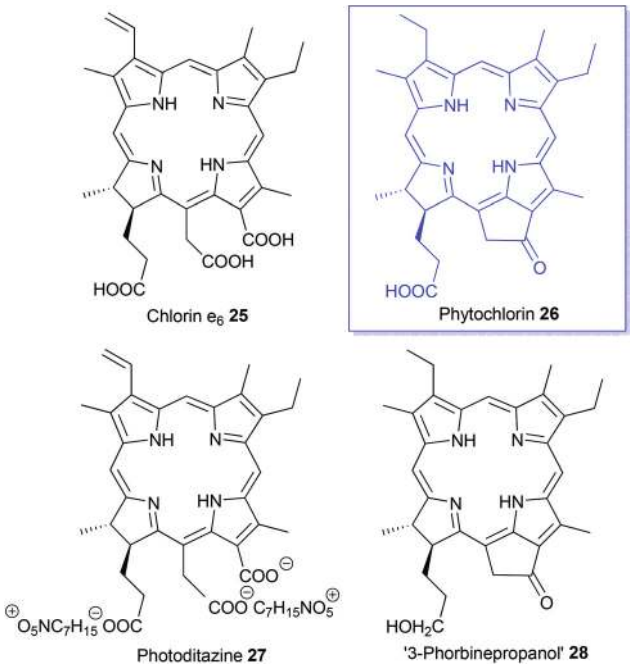


Fig. 12 Chlorin type photosensitizers derived from natural sources.

play an important role as PSs,[187,280,282] and their potential for the PDI of viruses have also long been known (Fig. 12).[54]

Photoditazine, a water-soluble glucosamine derivative of chlorin e_6 (**27**), has been used in an *in vitro* study against HSV to obtain a 1.5–2.5 log reduction of the virus titer.[283] The same compound had earlier been shown to be effective in a cervical cancer model associated with HPV 16, a HPV type known to have a high probability of leading to neoplastic lesions.[284]

Another chlorin derivative, 3-phorbinepropanol-9,14-diethyl-4,8,13,18-tetramethyl-20-(3*S-trans*) (**28**) was tested on the Bovine viral diarrhea virus (BVDV, enveloped virus) and the encephalomyocarditis virus (EMCV, non-enveloped) in the context of blood sterilization.[285] The chlorin was incorporated into liposomes which could then be immobilized on Sephacryl S-1000 beads. The enveloped BVDV was successfully inhibited in cell culture medium (4 log); however, this inhibition significantly decreased when human blood plasma was used.

Temoporfin, a synthetic chlorin PS [5,10,15,20-tetrakis(*m*-hydroxyphenyl)chlorin, **29**, Fig. 13], authorized in the European Union for the palliative treatment of head and neck cancer,[193] has been tested in the treatment of anal intraepithelial neoplasia related to HPV; however, it proved to be only partially effective.[286] *In vitro* PDT with Temoporfin was also found to alter Epstein–Barr virus (EBV) microRNAs and LMP1 protein expression in nasopharyngeal carcinoma cells carrying EBV, shedding light on the complex processes involved in virus-induced oncogenesis by EBV.[287] In a recent testing of a large cohort of medically active substances against the Zika virus, Temoporfin turned out to be one of the most effective. Notably, this effect was light-independent, suggesting that the compound itself may have antiviral properties against the Zika virus.[25b]

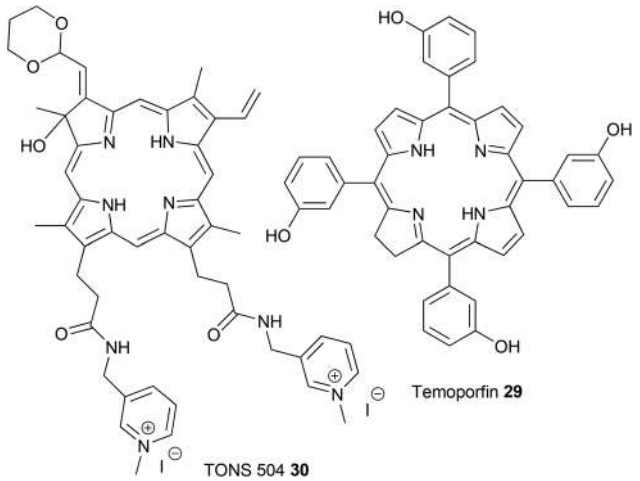


Fig. 13 'Synthetic' chlorin photosensitizers.

Recently, Latief *et al.* reported on the photodynamic inactivation of bacteria and viruses with the cationic chlorin PS "TONS 504" (**30**).[76] This PS was tested *in vitro* against an HSV-1 and two acyclovir-resistant strains of HSV-1. Complete eradication of the HSV strains could be achieved at a concentration of 10 mg L^{-1} and a light energy of 10 to 30 J cm^{-2}, and a concentration of 1 mg L^{-1} and a light energy of 20 or 30 J cm^{-2}, respectively.

3.6.3 Phthalocyanines. As with the other tetrapyrrole derivatives, phthalocyanines (**18**) have been evaluated for the photodynamic inactivation of viruses, beginning with studies on the inactivation of viruses in blood in 1991.[88,288] Their antiviral photodynamic activity has been discussed in general reviews on antiviral PDI.[7–9] Phthalocyanines have been evaluated for the PDI of a large number of viruses, among them most prominently VSV, HSV, and HIV. They showed high activity against these and other enveloped viruses[289–292] but were in general found not to be active against non-enveloped viruses,[289,290,292] suggesting that the viral envelope is a main target of the ROS generated. However, the non-enveloped human rhinovirus type 5 (RV-5) was successfully photoinactivated with a sulfonated naphthabenzoporphyrazine.[293] Simple tetrasubstituted phthalocyanines are conveniently accessible by tetramerization of the corresponding substituted phthalodinitriles, however this ease of synthesis is accompanied by the formation of all possible regioisomers during synthesis (*cf.*, Fig. 14, **31** and **35a/b**). The synthesis of specifically substituted compounds, such as the amphiphilic structures **32** and **34** (Fig. 14), requires different more sophisticated approaches.

Apart from their peripheral substituents the chemical and photophysical properties of phthalocyanines are also decisively determined by the central metal ion.[291] For example, a higher PDI was found for a zinc tetracarboxyphthalocyanine compared to the aluminum derivative.[291] In general, however, a clear tendency cannot be observed. The central metal ion of course influences the $^1O_2$ quantum yield,[290,291] which renders, *e.g.*, zinc or aluminum phthalocyanines as attractive PSs. Rywkin *et al.* identified a Type II mechanism as the predominant one for the PDI of VSV with aluminum phthalocyanine tetrasulfonate (Fig. 14).[88] On the other hand, metal phthalocyanines with lower $^1O_2$ quantum yields may act *via* a Type I mechanism. Sobotta *et al.* observed infectivity reduction for several viruses such as HSV-1, para-influenza virus 3, Punta Toro virus, Sindbis virus, and IAV with copper phthalocyanines, for which they found a low $^1O_2$ quantum yield.[290] Nevertheless, most investigations have been made with (substituted) silicon, aluminum and zinc phthalocyanines.

With respect to peripheral substituents different functionalizations have been investigated, *e.g.*, anionic (sulfonated), cationic, *tert*-butyl-, 1,4,7-trioxanonyl, and lysine-substituted compounds (generic structure **31**, for specific examples see **32–35**, Fig. 14), thereby also increasing the solubility of the phthalocyanines.[289b,290] Sulfonated compounds were found to exhibit a higher activity against VSV and HSV than non-sulfonated derivatives.[294a] However, partially sulfonated compounds were more active than the tetrasulfonated derivatives for the N2 retrovirus and vaccinia virus.[84] Allen *et al.* have tested this 'amphiphilicity concept' by introducing *tert*-butyl groups and combining them with sulfonation. Indeed, a higher activity for the more amphiphilic compounds was observed.[84,294b] High antiviral activities have been found for cationic phthalocyanines against, *e.g.*, VSV, HIV-1, and the Sindbis virus;[84,289a] however, some of these compounds were also active in the absence of light.[293,294] In a number of cases it has been shown that phthalocyanines can have an antiviral activity in the absence of light.[295–298]

Mostly, phthalocyanines have been investigated with respect to the antiviral PDI of blood products.[84,88,288,294,299,300] One silicon phthalocyanine, "Pc4" (**36**), was specifically developed and investigated for this purpose, as it showed high activities against HIV and VSV,[299,301] and was found to inactivate both cell-free HIV as well as actively replicating HIV and latently infected cells.[301]

Pc4 is also under investigation as a promising PS for tumor therapy.[187] The primary targets of PDI of VSV with Pc4 were analyzed and a very rapid decrease in viral RNA synthesis following photodynamic treatment was observed.[114] The phthalocyanine induced apoptosis in HIV infected cells.[302] Experiments aimed at investigating *in vitro* the possibility of activation of the HIV promoter *via* a photodynamic treatment showed that Pc4 was unable to do so, while UV-A excited 8-methoxypsoralen was successful. A range of studies on phthalocyanines reported optimization of the irradiation protocol, with the aim of maintaining the virucidal activity while reducing treatment-induced damage to red blood cells.[303–305] The photohaemolysis of human erythrocytes following photodynamic treatment with a ZnPc was analyzed by Zavodnik *et al.*[306] The use of protective agents against such damage to red blood cells was also evaluated; *e.g.*, employing a water-soluble vitamin E derivative or reduced glutathione. The latter was able to protect red blood cells from binding IgG following PDI with phthalocyanines.[304,307] This IgG binding is critical,

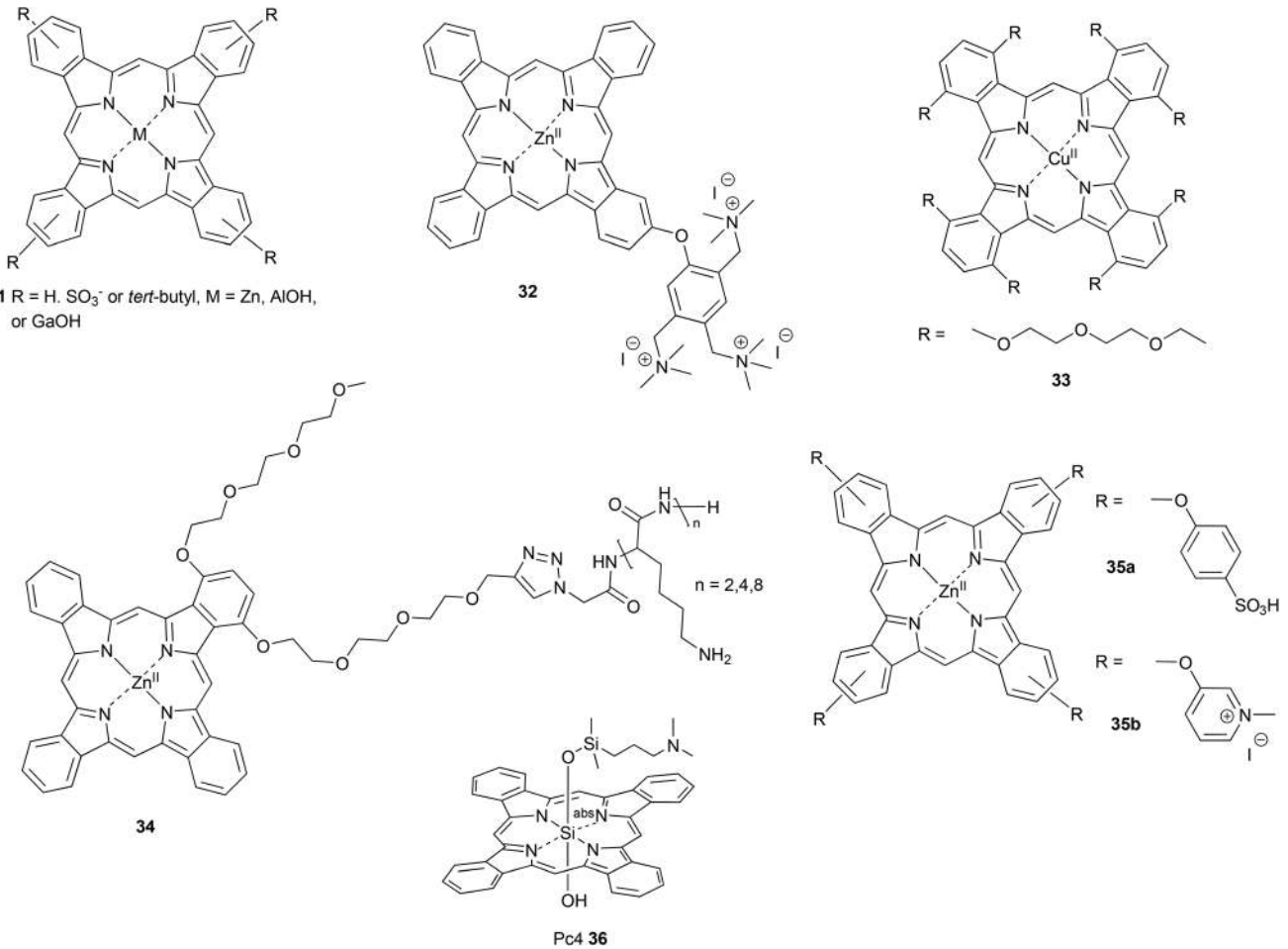


Fig. 14 Phthalocyanine photosensitizers.

as it can interfere with cross-matching tests performed prior to transfusion.

In addition to blood product disinfection, phthalocyanines have been proposed and tested for the inactivation of adenoviral vectors in the context of biosafety in laboratories using recombinant adenovirus vectors gene transfer and gene therapy.[308]

A few publications have addressed the targets of antiviral PDI with phthalocyanines.[87,309] For aluminum phthalocyanine tetrasulfonate it was elucidated by quenching experiments that $^1O_2$ plays the dominant role for VSV inactivation.[9] For the same compound, strong inhibition of viral RNA polymerase of VSV was detected after PDI; HPLC and electrochemical analysis detected the formation of 8-oxo-7,8-dihydroguanosine.[114,300] For an amphiphilic phthalocyanine major changes in the protein profile of HSV-1 after PDI were observed; specifically for glycoprotein D, one of the structural proteins of HSV-1.[87]

Particle-based formulations containing phthalocyanine PSs have also been tested for antiviral PDI. Silica up-converting nanoparticles loaded with ZnPc have been used against the DENV.[166,310] Recently, particle-based phthalocyanine PSs and cholinyl-substituted aluminum phthalocyanine loaded on silica gel were used for MS2 phage and poliovirus inactivation.[311]

3.7 Riboflavin

Riboflavin, or vitamin B2, (**37**, Fig. 15) is an essential vitamin in humans which generally acts as a co-factor for flavin coenzymes, playing an essential role in human cell metabolism.[312] Its potential role in the photoinactivation of microorganisms has been known for over half a century.[9,313]

As it is a naturally occurring compound in the human body, this facilitates the use of riboflavin for medical applications. From the beginning, the application of riboflavin in PACT and the PDI of viruses which has found most interest, and is still the most intensely investigated field, is the decontamination of blood products.[9,18b,314–316] Along with the psoralen derivative 4′-(4-amino-2-oxa)butyl-4,5′,8′-trimethylpsoralen (amotosalen) and the phenothiazinium dye methylene blue (*cf.*, below), riboflavin is one of the three photoactive dyes in standard clinical use for pathogen reduction in blood products. An overview on the approval status is given in two recent reviews,[18b,317] and there are numerous reviews detailing its application in blood

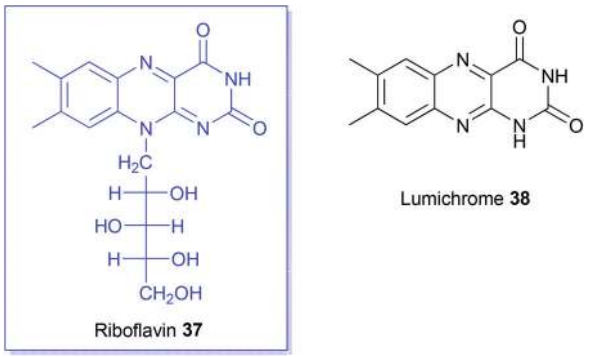


Fig. 15 Riboflavin.

decontamination.[18b,93b,316–321] The fact that over 100 million units of blood donations are collected each year underlines the medical importance of PDI and PACT for blood products.[317]

Due to the extensive knowledge of this naturally occurring compound, riboflavin has been qualified by the FDA as GRAS (Generally Regarded as Safe).[93b] It binds to the nucleic acid bases of DNA and RNA, and upon UV-irradiation, specifically oxidizes the guanine bases in nucleic acids by a single electron transfer reaction.[8,10,316,318a,322] In follow-up reactions, $^1O_2$, hydrogen peroxide and hydroxyl radicals are formed.[93b,316,318a] This results in irreversible single strand breaks in nucleic acids, damaging the pathogens.[316,318b,319] The primary photoproduct of riboflavin is lumichrome (**38**). Neither riboflavin nor its photoproducts need to be removed after treatment.[93b] Riboflavin has been shown to be effective against enveloped as well as a number of non-enveloped viruses – to include HIV, West Nile virus, VSV, IAV, porcine parvovirus, pseudorabies virus, human hepatitis A virus (HAV), encephalomyocarditis virus, Sindbis virus, the MERS coronavirus, among others.[18b,316,320–324] Riboflavin is the active PS in the MIRASOL Pathogen Reduction Technology System (Terumo BCT, Lakewood, CO, USA),[93b,325] which is used to treat platelet and plasma products.[18b,93b,317,323] Moreover, it is also in use for pathogen reduction in whole blood.[18b,316,317] Due to the strong absorption of visible and UV light by whole blood, methods suitable for other blood products are not simply transferable to whole blood (see section below on psoralens).[316,317] Preclinical[18b,323,326] and clinical studies[18b,327] have been performed with riboflavin/UV-treated blood products to assess its safety and efficacy and an overview is given in recent reviews.[18b,316,317,323,328]

As for all blood inactivation techniques one major interest is of course how the blood preparations are affected by the treatment.[18b,93b,316,317,320] For example, in a publication by Larrea *et al.* it was shown that, as also observed for other pathogen reduction procedures for plasma products, treatment with riboflavin and UV light reduced the activity levels of several pro-coagulant factors, whereas coagulation inhibitors were preserved.[329] An investigation on the photochemical inactivation of HBV with methylene blue and riboflavin showed the photochemical inactivation of HBV with riboflavin, in contrast to methylene blue, resulted in the loss of ability to regulate viral immunity, and to be related to the different photochemical inactivation mechanisms.[330] The riboflavin/UV treatment is able to inactivate residual donor leucocytes and T-cells.[93b,326,331] Recently, a decrease in platelet function with storage time was observed and this correlated with a decrease in the effectiveness of transfusions.[332]

Proteomics are now used as a tool to assess the changes to the proteome associated with the different methods of pathogen inactivation during storage of platelet concentrates.[316] Results have been summarized by Prudent *et al.* for a comparative evaluation on riboflavin/UV, amotosalen/UV-A, and UVC pathogen inactivation.[333] For riboflavin this is amended by a very recent study on protein changes occurring upon Mirasol riboflavin/UV treatment.[334] Semi-quantitative proteomics also emerged as a tool to differentiate between protein changes due to the riboflavin/UV treatment and the so-called platelet storage lesion.[334] Consistent with oxidative damage, riboflavin/UV-treated platelets exhibited an increase in the formation of ROS by day five of storage, and the NF-κB signaling pathway was also found to be activated in the treated platelets.[335]

One rare, possible serious complication after transfusion is the transfusion-related acute lung injury (TRALI).[336] In an *in vivo* study in BALB/c SCID mice it was shown that the riboflavin-treated whole blood did not produce lung injury after short storage. After longer storage development of a mild lung injury was observed; however, this was storage-dependent and was without significant differences to the control groups.[337]

3.8 Psoralens

Psoralen and its derivatives have long been known for their photosensitizing properties and for their potential application in the phototherapy of viruses.[338] Psoralen is a heterocyclic, tricyclic compound consisting of a furan and a pyrone ring (**39**, Fig. 16). Psoralens have an affinity to DNA and RNA and intercalate in nucleic acids. Upon activation with UV-A, covalent crosslinking to pyrimidine bases occurs.[18d,93] This results in the formation of mono- and di-adducts which are eventually responsible for the inactivation of viruses and bacteria.[93b,314,315] Its mechanism of action is different to that of other PSs, and 8-methoxypsoralen (**40**) is known to have

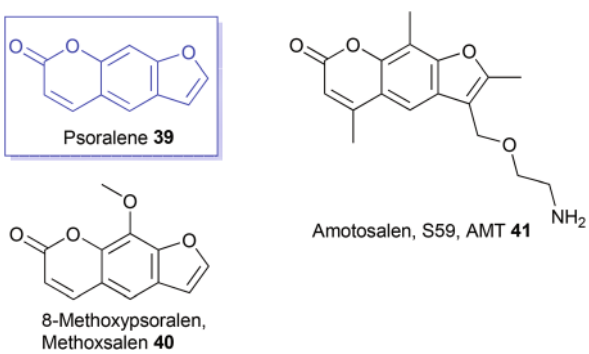


Fig. 16 Psoralen and derivatives.

mutagenic potential.[93] However, psoralens have also been found to generate $^1O_2$, hence, this pathway also contributes to their phototoxic properties.[39]

With respect to the PDI of viruses, many different psoralen derivatives have been evaluated, in an attempt to maintain the antiviral and antibacterial potential while at the same time lowering mutagenic potential and toxicity.[93b,339] From this research the compound 4′-(4-amino-2-oxa)butyl-4,5′,8′-trimethylpsoralen (Amotosalen, also S59, or AMT, **41**) has emerged as a promising development.[340]

Compared to 8-methoxypsoralen, amotosalen is more hydrophilic because of its amino group. The compound is water-soluble and can more easily pass through cellular membranes. Moreover, under physiological conditions it is cationic and therefore has an increased affinity to DNA.[93b,340b,341] Amotosalen is the active compound in the INTERCEPT Blood System (Cerus Corporation, Concord, CA, USA).[340,342] Recent publications on the PDI of viruses with psoralen derivatives have centered around amotosalen and its use in the decontamination of blood products.[18b,93b,316–321] As mentioned, amotosalen/UV-A treatment induces inter- and intra-strand cross-linking in nucleic acids, which is the mechanism responsible for the antiviral action. After the irradiation procedure, most of the amotosalen is photodegraded and a large portion consists of amotosalen dimers.[93b,341,343] In the INTERCEPT process, these and other photoproducts, as well as remaining amotosalen in the treated blood products, are removed or at least reduced in a subsequent filtering step.[316,341,343] The remaining amotosalen photoproducts were not found to induce neoantigen formation, lowering the probability of adverse immune responses.[344]

Amotosalen has proven to be active against a large number of both enveloped and non-enveloped viruses, *i.e.,* HIV, HBV, human T-lymphotrophic virus type I and II, cytomegalovirus (cell-associated), BVDV, West Nile virus, Chikungunya virus, IAV, SARS Corona virus, DENV, Crimena-Congo hemorrhagic fever virus, Parvo virus B19, blue tongue virus, human AdV, the Zika virus, and others.[18b,d,320,321,340b,345,346] For DENV inactivated with amotosalen/UV-A, an *in vitro* study showed that the inactivated viruses keep their immunogenicity, *i.e.*, they provoked T-cell responses similar to that of non-inactivated viruses.[346] Later it was shown that the same holds for other viruses, *e.g.*, the Crimean-Congo hemorrhagic fever virus, Lassa virus, MERS virus and the Rift Valley Fever virus.[18d]

The development of the amotosalen-based blood disinfection approach involved a range of studies on the pre-clinical safety and clinical efficacy of the product. A concise overview is given in recent reviews.[18b,320,340b] A description of multi-center clinical trials can be found in the review by Schlenke,[18b] while the toxicology testing has been summarized by Dayan[341] and others.[18b,347] One issue in the safety-testing was of course genotoxicity. In this respect, a review on the genotoxic potential of the amotosalen/UV-A pathogen reduction technology and the assessment of the possible hazards in recipients of treated platelets concluded that the mutagenic hazard to recipients of treated platelets is negligible. Any observed genotoxic effect in the *in vitro*/*in vivo* tests at high concentrations could be attributed to residual amotosalen.[347]

The results from the two recent phase III trials on amotosalen-treated platelet products were published in 2010[348] and 2011.[349] The later study involved a randomized, controlled, double-blind trial to evaluate the efficacy and safety of amotosalen-treated platelet components stored for 6–7 days *vs.* conventional platelet components (non-inferiority design), and showed the non-inferiority of the amotosalen-treated platelets. In the former study a higher rate of adverse events (bleeding events) was found for the amotosalen-treated product. However, there has been some discussion in the literature about the evaluation of the bleeding events and the study design,[18b,c,350] and this is also evaluated in a meta-analysis of all five main phase III studies.[351] In a survey on the occurrence of adverse events with four types of fresh-frozen plasma in France (in the last 10 years), comprising two phototreatment methods (amotosalen/UV-A and methylene blue/light, *vide infra*) along with two other types (solvent-detergent[316] and quarantine) all four types were found to be associated with low occurrences of adverse events (7.14–1.05 adverse events per 10 000 deliveries).[352] A low occurrence rate for adverse events with amotosalen/UV-A-treated blood products was also stated in two recent reviews taking into account data from post-marketing studies and a review based on application data in the USA.[353] A recent retrospective analysis study with 306 patients in need of massive transfusion observed no negative effects on clinical outcomes, in-hospital mortality, and length of stay.[354]

One of the serious possible complications of transfusion is the graft-*versus*-host disease, which is caused by T lymphocytes of the donor. As photoinactivation techniques can inactivate proliferating T-cells, the use of blood components treated in this manner may be a measure to lower the risk of this complication. A recent review concludes that amotosalen/UV-A-treated blood products may indeed serve this purpose.[355]

The effects of amotosalen/UV-A on platelets and blood products have, of course, also been analyzed and summarized in a number of publications.[333,340] These investigations hinted to a reduced platelet function following amotosalen/UV-A treatment and the mechanism for this has recently been investigated by Stivala *et al.*[356] The authors concluded that the amotosalen/UV-A treatment induced platelet p38 activation, glycoprotein Ib shedding and eventually platelet apoptosis by a caspase-dependent mechanism. As a result, platelet function and survival are reduced. Thiele *et al.* compared the effects of amotosalen/UV-A treatment and gamma-irradiation by proteomics based on an LC-ESI-MS/MS analysis.[357] It was found that gamma irradiation initially caused more alterations in the platelet proteome than amotosalen/UV-A. However, this effect was reversed after five days of storage. After this period there were more changes in the amotosalen/UV-A treated platelets, hinting at enhanced storage lesions in the amotosalen/UV-A treated platelets.

The amotosalen/UV-A procedure is not applicable in whole blood due to the color and strong absorption of the latter, which would require unacceptable high intensities of UV light.

Hence, a method has been developed for whole blood that does not rely on photoinactivation, but acts *via* a bis-alkylating agent to crosslink nucleic acids.[358] The compound amustaline [[*N*,*N*-bis(2-chloroethyl)]-2-aminoethyl-3-[(acridin-9-yl)amino] propionate dihydrochloride], an acridine **42** derivative, (**43**, Fig. 17) used in combination with glutathione, is currently in clinical development.[314,315,327,358,359] This inactivation corresponds to other chemotherapeutic viral inactivation methods such as beta-propiolactone, which is commonly used for pathogen inactivation in vaccine preparations.[360]

3.9 Phenothiazines and methylene blue

Phenothiazines (**44**) and among them the most prominent compound, methylene blue (**45**), are perhaps the best-known antibacterial and antiviral PSs (Fig. 18). Investigations on their antiviral activity date back to the beginning of the 20th century, with the observations of Oscar Raab[48] and investigations in the 1920s.[361,362] The antibacterial and antiviral activity of phenothiazinium PSs has been extensively reviewed, specifically for this compound class,[56,362–365] and also as part of general reviews on pathogen inactivation.[2,7a,8a,9–11] A large number of structural modifications on methylene blue and its congeners have been reported, including straightforward modifications as well as reactions, *e.g.*, substituting sulfur with selenium thereby yielding selenoxanthylium PSs.[366]

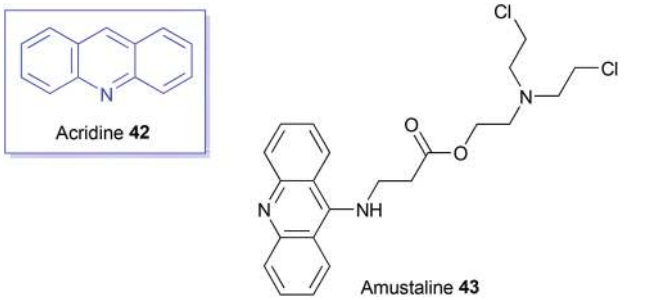


Fig. 17 Amustaline.

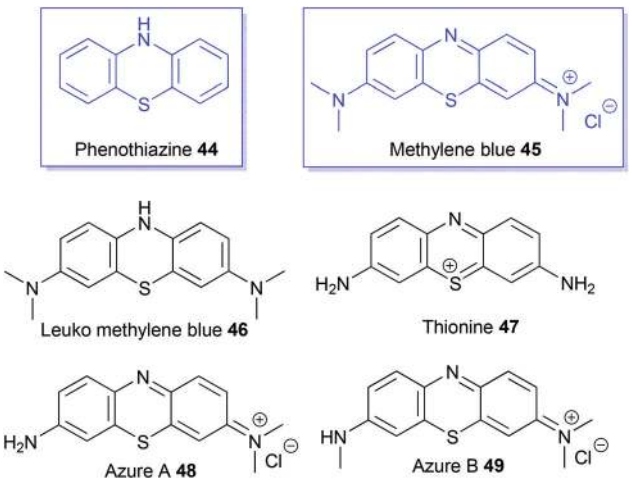


Fig. 18 Phenothiazines and photooxidation productions of methylene blue.

In the 1970s, phenothiazine derivatives were used to treat herpes infections; however, these trials were overshadowed by the occurrence of Bowen's disease in some patients which has been attributed to the interaction of the PS with viral DNA provoking oncogenic effects.[9,362,367] That said, there are still examples of successful treatment of HSV using methylene blue.[367f,g] Later work has focused on the application of phenothiazine derivatives in the pathogen inactivation in blood products, with methylene blue as the lead compound.[56,363,364] One reason for the prominent role of methylene blue is the acquired clinical evidence on its safety in humans after long term use in the treatment of methemoglobinemia.[56] Today, methylene blue/white light is routinely used for blood product disinfection.[93b,316,318,319,320,321] Introduced in 1991,[18c] the current approval status is given in recent reviews.[18b,317] The methylene blue/light treatment is also one of the standard procedures mentioned in a WHO report on viral inactivation and removal from blood products.[368]

Nevertheless, though mainly used for blood product disinfection, recent clinical reports are related to the treatment of virus infections by methylene blue/light (*vide infra*).[369] Methylene blue is known to bind to DNA, either to the outer helix or by intercalation, especially in guanine- and also cytosine-rich regions.[8a,56,93b] The dye is known to undergo Type I as well as Type II photoreactions.[56,93b,364] Direct electron transfer is probable, leading to DNA strand breaks in the absence of oxygen or at low oxygen concentrations. In the presence of oxygen, photooxidations occur *via* a Type II mechanism; this has been proven by the formation of 8-hydroxyguanine in nucleic acids upon methylene blue phototreatment.[56] The damage resulting from Type I and Type II photoreactions is not limited to DNA/RNA, as methylene blue also damages viral surface structures such as proteins. Methylene blue itself is degraded to partially demethylated products (Azure A and B), leukomethylene blue and thionine (**46–49**).[93b] When two RNA viruses, Sindbis virus and HCV were treated with methylene blue/light, followed by nucleic acid amplification to determine RNA lesions, the nucleic acid amplification of the treated viral RNA was found to be inhibited in a time-dependent manner.[95] As the inhibition of RNA amplification for the Sindbis virus was to be directly correlated with a loss of *in vitro* infectivity, the authors concluded that RNA was the main target of methylene blue/light inactivation in this case.[95]

Because of its longstanding use as a PS, methylene blue has been effectively tested against a large number of viruses, overviews are given in the aforementioned reviews.[56,362–365] This list is constantly expanding,[370–372] in response to new medical needs as exemplified, *e.g.*, with testing methylene blue/light for enterovirus 71 or Zika virus inactivation.[370b,372] As mentioned above (section 3.7 riboflavin) it was shown that the immunogenicity of hepatitis B is retained after photochemical inactivation of HBV with methylene blue.[29,330]

Commercially, methylene blue is used as the active substance in the THERAFLEX MB Plasma system (Macopharma,

Tourcoing, France).[18c,373,374] An older similar method also using methylene blue is referred to as the 'Springe method'.[93b,373] Prior to the addition of methylene blue in the form of a dry pill, the plasma is filtered to reduce, among other things, the levels of remaining blood cells, intra-cellular viruses and microparticles. After illumination, a second filtration step has been introduced to reduce the residual amount of methylene blue and its photoproducts.[93b,374b,375] The THERAFLEX MB procedure has been found to be active against enveloped as well as non-enveloped viruses such as HIV, West Nile virus, BVDV, pseudorabies virus, IAV, Sindbis virus, porcine parvovirus, porcine encephalomyocarditis virus, HCV, Zika virus, DENV and Chikungunya viruses.[18b,370] The THERAFLEX MB system has been analyzed in a number of comparative reviews together with the MIRASOL (riboflavin) and the INTERCEPT (amotosalen) system.[93b,316–321]

The previously mentioned analysis by Bost *et al.*[352] found methylene blue/light (as amotosalen) to be associated with only low occurrences of adverse events. In 2007, Politis *et al.* compared fresh-frozen, leuco-reduced plasma inactivated with methylene blue/light (THERAFLEX MB) to non-methylene-blue-treated plasma with respect to safety and efficacy after 5 years of clinical experience.[376] The coagulation factor losses remained in the accepted range, the rate of occurrence of adverse reactions was lower in the methylene blue-treated plasma group (though the data basis for the untreated plasma was of course much broader), and no seroconversions for infectious diseases were reported for the methylene blue-treated plasma group.[376] This safety profile was confirmed in a follow-up study in 2014.[18c,377]

In an *in vitro* study on the quality of methylene blue-treated plasma (THERAFLEX MB) stored for up to 27 months the authors measured coagulation-related parameters (*i.e.*, several coagulation factors, inhibitors of proteins C and S, and antithrombin and activation markers).[378] They observed a decrease in clotting factors which remained, however, in the range found for healthy subjects. The authors concluded on a safe storage period of 2 years.[378] A subsequent study analyzed the recovery of factor VIII and fibrinogen from plasma samples obtained from whole blood and apheresis donations and treated with the THERAFLEX MB system.[379] The mean factor VIII level after treatment exceeded 0.5 IU mL^{-1} in all series and varied between 78% and 89% in the different series. For factor VIII, the recovery was found to be dependent on plasma source. The mean levels of fibrinogen after treatment exceeded 200 mg dL^{-1} in all series, with the level of fibrinogen after treatment correlating with the level prior to treatment.[379]

A few years ago, the bacterial and viral reduction capacity of the THERAFLEX MB system was compared in a challenge study with a series of bacteria and viruses in lipaemic plasma.[380] The authors concluded that the system was effective in bacterial reduction mainly because of the integrated filtration system, the remaining bacteria were effectively reduced by the methylene blue/light treatment. Viral reduction *via* the THERAFLEX MB system was able to effectively compensate for lipaemia.[380] Last year, the same group investigated the effect of plasma temperature on viral inactivation capacity and plasma quality of methylene blue/light-treated plasma.[381] They tested three temperatures (5, 22, and 30 °C) using three viruses (Suid herpes virus, BVDV and VSV). Viral inactivation was significantly decreased at 5 °C. At higher temperatures the photocatalytic degradation of methylene blue was increased.[381]

Though being in standard clinical use, there are doubts over the use of methylene blue/light-treated plasma for patients receiving multiple plasma donations, *e.g.*, in the case of patients suffering from thrombotic thrombocytopenic purpura.[18c,382] Moreover, there have been reports on severe allergic reactions following the administration of methylene blue/light-treated plasma.[18c,383] As a result of these concerns and the evaluation of the data, the authorization for the THERAFLEX MB system was withdrawn in France in October 2011 by the health authorities.[18c,352] Other evaluations did not find an increase in severe allergic reactions.[18c,384] A position statement from the UK [Joint UKBTS/HPA Professional Advisory Committee/Serious Hazards of Transfusion (SHOT)] on the issue recommended no immediate withdrawal but a close, proactive monitoring of reaction rates to methylene blue/light-treated plasma.[385] The company marketing THERAFLEX MB has also developed an alternative treatment method which does not make use of a photosensitizing agent, but relies on irradiation with UV-C to achieve pathogen reduction (THERAFLEX UV-C). The current clinical and regulatory status of this system has been summarized in recent reviews.[18b,93b,317,352,370a,b,386] Results from a phase I study with this system for pathogen inactivation in platelet concentrates have been published.[387]

3.9 Other photosensitizers

Naturally, there is a variety of other organic PS structures for which investigations on the PDI of viruses have appeared in recent years, partly covered in the general reviews.[8a,9,10] These include PSs that have long been known but are not so much in the current focus of the PDI of viruses, such as Rose Bengal (**50**),[388,389] cyanine dyes[390] or rhodamine B (**51**), and derivatives such as octadecyl rhodamine B ('R18', **52**),[112] as well as new structures (Fig. 19)[105a,109,110] or multicomponent plant extracts.[104] In the following section, a selection of contemporary studies and new approaches will be presented.

One compound that has attracted considerable interest in the PDI of viruses is 1,5-iodo-naphthylazide (also referred to as INA, **53**).[106] INA is a photoinducible alkylating agent active against enveloped viruses.[105] As a hydrophobic compound, INA is incorporated into the lipid bilayers of virus envelopes. When activated by light (UV-A) photoinduced alkylation of proteins in the lipid bilayer occurs.[105–107]

A few years ago, INA was also found to inactivate Encephalomyocarditis virus (EMCV), a non-enveloped virus.[391a] In this case, an association of INA with the viral RNA was observed. With its mechanism of action, INA was able to inactivate the virus but maintain its structural integrity and antigenicity, thus keeping its ability to provoke a competent

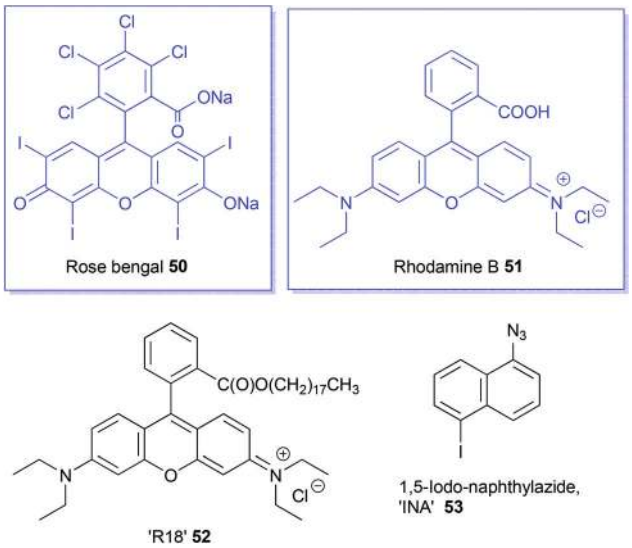


Fig. 19 Examples of other compounds tested for the PDI of viruses.

immune response. Treatment of mice with INA/light-inactivated Zaire Ebola virus was found to protect the mice if they were subsequently challenged with an otherwise lethal dose of the untreated virus.[106] The same was demonstrated for the Venezuelan equine encephalitis virus (VEEV).[391b] Viral inactivation, while maintaining virus structure and immunogenicity, has also been shown for preparations of the IAV and DENV.[107,346]

INA/UV-A and amotosalen/UV-A were compared in the inactivation of alpha and pox viruses, and both procedures effectively eliminated viral infectivity, though amotosalen proved to be more active than INA on vaccinia and pixuna viruses.[392] Belanger *et al.* have studied the effect of different iodo- and azido-substituted naphthalenes and UV-A irradiation on HIV-1. For prolonged irradiation times (15 min, compared to 2 min) with the aryl azides they observed the additional effect of viral protein aggregation which they attribute to ROS formation based on photochemical conversion of the azido-substituted naphthalenes.[105]

Development and structural optimization of PSs obviously will always address the question of PS affinity to the intended target of PDT or PDI (tumor cells, bacteria, viruses). The other important aspect of optimization is the photophysical and photochemical part of PDT and PDI, *i.e.*, the generation and release of $^1O_2$ and other ROS. In anti-tumor PDT, a recent approach involves the 'storage' or retarded release of $^1O_2$ *via* the reversible formation of endoperoxides with suitable aromatic moieties,[121] *e.g.*, with pyridone-appended porphyrins (**54**, Fig. 20).[393] This 'storage' and thermal release of $^1O_2$ has also been investigated for the PDI of viruses.[394,395] Dewilde *et al.* used a water-soluble naphthalene derivative (**55**) to effectively inactivate the enveloped viruses HIV 1, HSV type 1, cytomegalovirus, and VSV, evidencing that $^1O_2$ plays an important role in the inactivation of these viruses, as the thermally generated $^1O_2$ excludes Type I photoreactions. The naphthalene

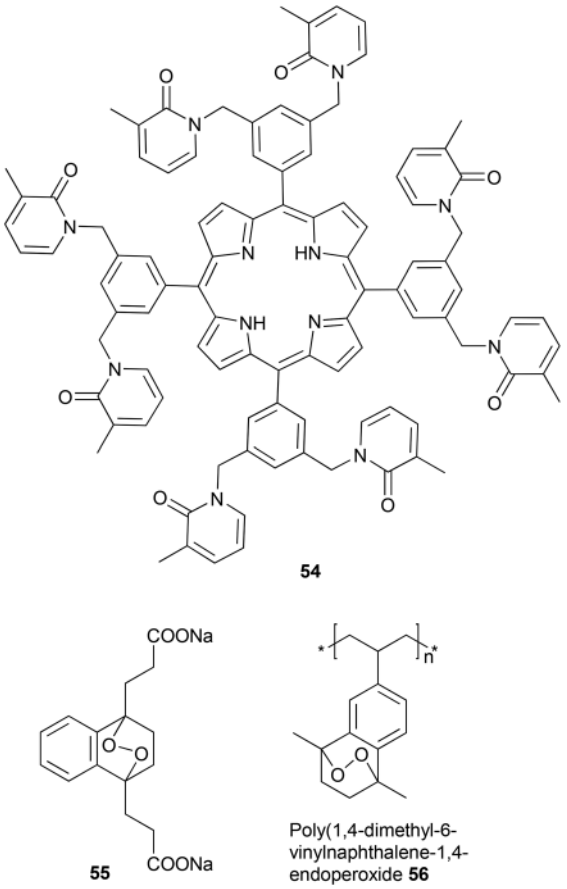


Fig. 20 Systems for 'storage' and retarded release of $^1O_2$ in anti-tumor PDT and for the PDI of viruses.

derivative was, however, inactive against the non-enveloped viruses, adenovirus and poliovirus 1.[394] In a similar approach, Käsermann and Kempf used a polymeric naphthalene endoperoxide compound (**56**) to thermally generate $^1O_2$ to show its ability to inactivate the enveloped viruses SFV and VSV. As the endoperoxide compound is water-insoluble it can be removed from water-based solutions after the heterogeneous reaction.[395]

With respect to vaccine development, as well as related to the study of viral action mechanisms, it is often desirable to inactivate a virus but at the same time maintain certain functions of the virus for further studies. For example, octadecyl rhodamine B (**52**) has been found to deprive the Sindbis virus of its infectivity while maintaining its ability for membrane fusion.[112] A photoactive analogue of the reverse transcriptase inhibitor Nevirapine **57**, 9-azido-5,6-dihydro-11-ethyl-6-methyl-11*H*-pyrido[2,3-*b*][1,5]benzodiazepine-5-one (**58**), was used to inactivate the reverse transcriptase of HIV-1, but preserved the conformational and functional integrity of viral surface proteins (Fig. 21).[109]

In 2010, a new broad-spectrum antiviral compound, termed 'LJ001', an aryl methyldiene rhodanine derivative (**59**, Fig. 22), was described.[396] It was active against more than 15 different enveloped viruses, including Ebola virus, Marburg virus, IAV,

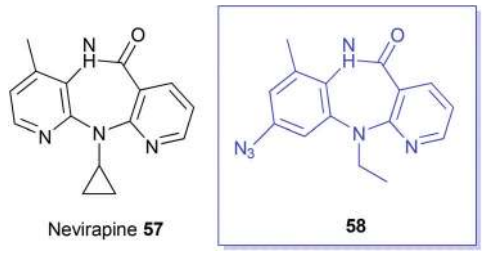


Fig. 21 Nevirapine and a photoactive analogue used for inactivating reverse transcriptase of HIV-1.

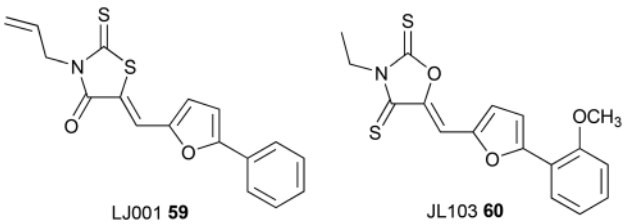


Fig. 22 LJ001, an aryl methyldiene rhodanine derivative, active *in vitro* as a broad-spectrum antiviral and the optimized compound JL103, an oxazolidine-2,4-dithione.

HIV, Yellow fever virus, HCV, West Nile virus and VSV.[396] Its effect was found to be based on the structural differences between more flexible cell membranes *vs.* more static viral membranes. LJ001 targets the viral lipid membrane and inhibits virus-cell fusion. The specific effect of the compound on the viral membrane has been elucidated in a publication from 2013 by Vigant *et al.*[110]

The molecular mechanism of LJ001 was found to be dependent on the presence of oxygen and light. The antiviral activity of could be suppressed by $^1O_2$ quenchers (sodium azide, 9,10-dimethylanthracene) or antioxidants (α-tocopherol), suggesting that LJ001 acts as a Type II PS. $^1O_2$ results in allylic hydroxylation of double bonds in the unsaturated phospholipids of the virus membrane. This removal of double bonds and the concurrent introduction of hydroxyl groups in the lipid membrane core changes the biophysical properties of the viral membrane (disturbing membrane curvature and fluidity), hindering virus-cell fusion.[110] LJ001 did not induce damage in cellular membranes, which the authors attributed to the cytoprotective system of eukaryotic cells against lipid peroxidation. Having elucidated this action principle and based on the drawbacks of LJ001 for *in vivo* application (*i.e.*, limited stability), a new class of antiviral PSs was developed. These oxazolidine-2,4-dithiones, with red-shifted absorption spectra and higher $^1O_2$ quantum yields showed an increased *in vitro* potency. One of the improved structures, 'JL103' (**60**) is shown in Fig. 22.[110]

The same research group also reported on the action mechanism of an antiviral compound belonging to the group of so-called rigid amphiphatic fusion inhibitors.[111] This compound, 'dUY11' (**61**, Fig. 23), combines a large hydrophilic head group connected to a rigid and planar hydrophobic

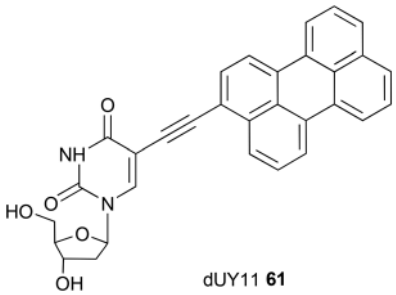


Fig. 23 dUY11, a rigid amphiphatic fusion inhibitor, whose antiviral activity is dependent on light and oxygen.[111]

moiety which inserts into the viral membrane. The action of these compounds is thought to be based on their similarity in shape to lysophospholipids, which play a decisive role in virus-cell fusion. However, looking at the antiviral effect of dUY11, the authors found that it is dependent on light and oxygen, *i.e.*, the inhibition of virus infectivity is absent in the dark and can be suppressed by the addition of a $^1O_2$ quenchers (NaN_3). Thus, dUY11 seems to be active *via* irradiation of its perylene moiety.[111]

The latter example sheds light on an intriguing (and complicated) aspect of the PDI of viruses: there are known PSs which may act *via* light-independent antiviral mechanisms (*e.g.*, Temoporfin, **29**). On the other hand, there may also be compounds with an undiscovered antiviral phototoxicity. This phototoxicity of known drugs is a general issue with regards to pharmacovigilance, *e.g.*, the well-known statin Atorvastatin has been found to generate $^1O_2$.[397] The EMA [European Medicines Agency] has published specific guidelines to address this phototoxicity as a side-effect of known drugs.

BODIPYs or boron-dipyrromethenes (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes) have found wide-spread application as fluorescent markers.[398] With specific substitution patterns minimizing fluorescence and enhancing intersystem crossing to the triplet state, BODIPYs can also act as PSs, thus a variety of BODIPYs have been investigated for use in PDT.[170,399] In this respect, the PDI of viruses has been addressed as well. For example, Carpenter *et al.* prepared the cationic BODIPY derivative **62** (see Fig. 24) and tested it against the inactivation of several bacterial strains and three viruses (DENV, VSV, and

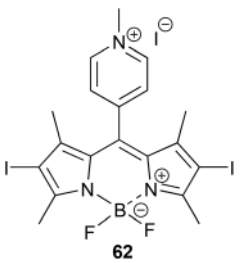


Fig. 24 A cationic BODIPY derivative with antibacterial and antiviral activity.[400]

human AdV5) in the context of antimicrobial photodynamic materials.[400] Infectivity reduction with the BODIPY was highest (6 log units) in DENV, followed by VSV (5 log units), and human AdV5 (2 log units).

These *ex vivo* decontamination applications for the PDI of viruses constitute a field of continuous interest for antiviral PSs, specifically for PSs that have long been known for their antimicrobial and antiviral activity (*e.g.*, Rose Bengal).[103,401] In this respect Rose Bengal has recently been proposed for the decontamination of wash water, using *Escherichia coli* BL21 and the bacteriophage T7 as model organisms.[389] One advantage of these long-known PSs is the acquired knowledge on the toxicity and biological effects, facilitating application development.

4. Conclusion and outlook

In this review it was our intention to give an overview on the PDI of viruses roughly covering the last decade to identify lines of development and current fields of application. A multitude of different viruses have been shown to be susceptible to PDI in *in vitro* investigations. These investigations encompass long-known viruses but have also taken up challenges faced by newly emerged viruses and viral diseases, *e.g.*, very recently with the case of the Zika virus. However, it is a long way from effectively killing viruses in suspension to a treatment in patients or elimination of viruses in complex media, such as blood products. A significant amount of clinical data on the PDI of viruses with different PSs and for different indications acquired years ago favored the bright prospects associated with phototreatment, whereas later this has focused more on specific applications and certain PSs already authorized for medical use.

With respect to PS development there is of course an ongoing interest in 'classical' PSs along the lines of phenothiazines, psoralens, tetrapyrroles (phthalocyanines, porphyrins), or riboflavins. Here, structural variations have been implemented and promising lead structures have been identified, *e.g.*, amphiphilic cationic porphyrins which have been intensely investigated.[10,75] Another interesting aspect is that the phototoxic effect of (well-known) PSs can in some cases easily be enhanced by combination with simple inorganic salts.[165] Such combinations could facilitate the development of products for the PDI of viruses under a regulatory aspect. New compound classes which have been explored for their potential in PDI of viruses include carbon materials or, recently, the aryl methyldiene rhodanine derivatives or oxazolidine-2,4-dithiones.[111] The elucidation of the mechanism of the rhodanine derivatives, which turned out to be based on photooxidation of virus envelope lipids, points to an important aspect in the PDI of viruses: compounds found to be active against viruses may have an undiscovered photodynamic action mechanism, and on the other hand there may also be 'classical' PSs (see Temoporfin)[25a] with a light-independent antiviral activity.

This underlines the requirement to assess the mechanism of antiviral activity for individual PS classes and individual PSs. Such specific investigations on the mechanism of antiviral activity (for example, discerning between Type I and Type II photosensitization) have appeared for a multitude of individual PSs and the current status on mechanistic investigations has been summarized in recent reviews.[8a,10,204] Different antiviral mechanisms can be relevant for one compound class, *e.g.*, fullerenes which act *via* Type I and Type II photosensitization but also show light-independent antiviral activity, or curcumin and hypericin which act as PSs but also show significant dark toxicity effects.[122b,142,143]

On the other hand, the psoralen derivative amotosalen, commercially applied in blood product decontamination, and 5-iodo-naphthylazide are examples for compounds which are photochemically active against viruses but do not rely on ROS for their antiviral effect. In general, the 'unspecificity' of the action of $^1O_2$ and other ROS generated by PSs (or positively phrased, their 'multi-target' mode of action) is seen as an advantage with respect to possible resistance formation given the genetic flexibility of viruses and bacteria.[14] The decade covered herein has seen first systematic investigations with respect to resistance formation in the PDI of viruses. For example, in a series of ten consecutive cycles of PDI against a bacteriophage with the cationic porphyrin **21** no development of resistance was observed.[203] This supports the hope that the PDI of viruses is an option even for newly emerging strains of known viruses.

The nearer PS development gets to a medical/clinical application, the question of adequate pharmaceutical formulations becomes more important. For tumor therapy, the usually lipophilic PSs have been incorporated into suitable carrier vehicles, often nanoparticles.[21a,c,22a,b] With ALA, the treatment of HPV infections and its manifestations usually involves the same formulations as employed in tumor therapy. For other PSs used for PDI, (nano)particle preparations have been tested mostly *in vitro*, such as silica particles for phthalocyanines,[310,311] nanoporous alumina or polyacrylonitrile nanofibers for porphyrins,[208,219] liposomes for chlorins and phthalocyanines,[285] or different nanostructured composites based on carbon materials.[96,179,180,183–185,218] However, related to the PDI of viruses, the merging of PS and particles can also serve a different purpose: important fields for the application of PDI do not intend an administration directly to the patient, notably and most prominently the decontamination of blood products. Here, particle-based formulations may be advantageous as they can serve to inactivate viruses and may then be removed by adequate filter systems.[96,285]

Currently, there are three main medical and clinical areas for the PDI of viruses: the treatment of local HSV infections and the treatment of HPV infections (viral warts) with authorized PSs; predominantly ALA, but also HPD or methylene blue. A growing number of clinical investigations on PDI against HPV manifestations has appeared in recent years. Particularly, the clinical treatment of *Condylomata accuminata* has been investigated in detail. However, the field with

the most practical relevance is probably the area of blood product decontamination. For this reduction/removal of viruses (and bacteria) from blood products, three PSs are in commercial use: Riboflavin, methylene blue, and the psoralen derivative amotosalen.[18b,c] Notably, two variants have been developed which do not rely on a PS: the alkylating agent amustaline (as a complement to amotosalen), which functions without light and can be used in whole blood, and, as a complement to the methylene blue/light treatment of blood products, the use of UV-C radiation.

Apart from this, the PDI of viruses has been investigated for several other medical applications such as eliminating the infectivity of viruses while maintaining their antigenicity/immunogenicity to provoke an immune response after vaccination or the use of PDI for the treatment of viral infections in animals, *e.g.*, for fish-farming plants.[18e,29,402]

Recent years have seen a growing interest in non-medical applications of the PDI of viruses.[196] For example, PDI has been proposed for food treatment,[128b,402c,403] which is attractive as naturally occurring PSs such as curcumin or riboflavin are present in some food products anyway.

With respect to public health and viral safety a number of publications deal with the elimination of viruses from air/water using PDI,[75,202,219] and the development of self-sterilizing materials and surfaces based on PS-loading.[206,208,404] Specifically, inorganic materials have been evaluated in this context.[162b,405,406] The use of inorganic materials, namely if employing inexpensive and environmentally friendly materials and sunlight as the natural light source offers considerable potential for this application of PDI. One example using a simple, inexpensive inorganic compound and sunlight is TiO_2 photocatalysis for PDI of viruses.[161,162] However, nanoparticle-sized TiO_2 – occurring in an multitude of products – is investigated for potential health issues.[407] In the context of viral safety, PDI has been proposed for the inactivation of viral samples in laboratory safety,[18d] and the PDI of viruses and bacteria has even been discussed as a measure for the destruction of biowarfare agents.[4,163] Further investigations of such applications are to be foreseen.

The most used medical application of the PDI of viruses is currently the field of decontamination of blood products. However, with the application of ALA specifically against HPV manifestations, the PDI of viruses has also found entrance into clinical practice.

Looking at this multifaceted field of antiviral phototherapy, it becomes apparent that there is not 'one' specific PS or class of PS which is best suited for the PDI of viruses, but that it always depends on the specific application and virus target.

Significant knowledge has been acquired in mechanistic investigations related to the PDI of viruses, elucidating the relative importance of Type I and Type II photochemical processes. The principal mechanism of action of the PDI of viruses due to the unspecific action of ROS implies a low probability of resistance development and initial investigations on resistance development support this. Notably, several publications report a light-independent antiviral activity for some compound classes (*e.g.*, fullerenes, tetrapyrroles). This is an interesting aspect for further investigations, as light-independent antiviral activity bears at least the principal option of a systemic application against viruses. In summary, given the rise of resistance against antivirals and the low probability of resistance formation, the PDI of viruses is a valuable support for the arsenal against viral diseases.

Abbreviations

AdV	Adenovirus
ALA	δ-Aminolevulinic acid
BoHV	Bovine herpes virus
BVDV	Bovine viral diarrhea virus
Cox	Coxsackie virus
DENV	Dengue virus
EBV	Epstein Barr virus
EIAV	Equine infectious anemia virus
EMCV	Encephalomyocarditis virus
FCV	Feline calivirus
FHV	Feline herpes virus
FVC	Feline corona virus
HA	Haemagglutinin
HAL	Hexaaminolaevulinate
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMME	Haematoporphyrin monomethyl ether
HPD	Haematoporphyrin derivative
HPV	Human papilloma virus
HSV	Herpes simplex virus
IAV	Influenza A virus
IFN	Interferon
ISC	Intersystem crossing
JEV	Japanese encephalitis virus
MAL	Methyl aminolevulinate
MIV	Mosquito iridovirus
MNV	Murine norovirus
NDV	Newcastle disease virus
NIR	Near infrared
NP	Nanoparticle
NV	Norovirus
SFV	Semliki Forest virus
SOD	Superoxide dismutase
PACT	Photodynamic antimicrobial chemotherapy
PCI	Photochemical internalization
PDI	Photodynamic inactivation
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PEI	Polyethyleneimine
PpIX	Protoporphyrin IX
PS	Photosensitizer
PVP	Polyvinylpyrrolidone
ROS	Reactive oxygen species

RV	Rhinovirus
SFV	Semliki forest virus
TNF	Tumor necrosis factor
UCNP	Up-conversion nanoparticles
VEEV	Venezuelan equine encephalitis virus
VSV	Vesicular stomatitis virus
ZnPc	(Phthalocyaninato)zinc(II)

Conflicts of interest

A. Wiehe is employee of the biolitec research GmbH which belongs to the biolitec group. The biolitec Pharma GmbH, which is also part of the biolitec group, is the marketing authorization holder for the medicinal product Foscan® which contains the photosensitizer Temoporfin as the active substance.

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