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Phototherapeutic Anticancer Strategies with First-Row Transition Metal Complexes: a Critical Review

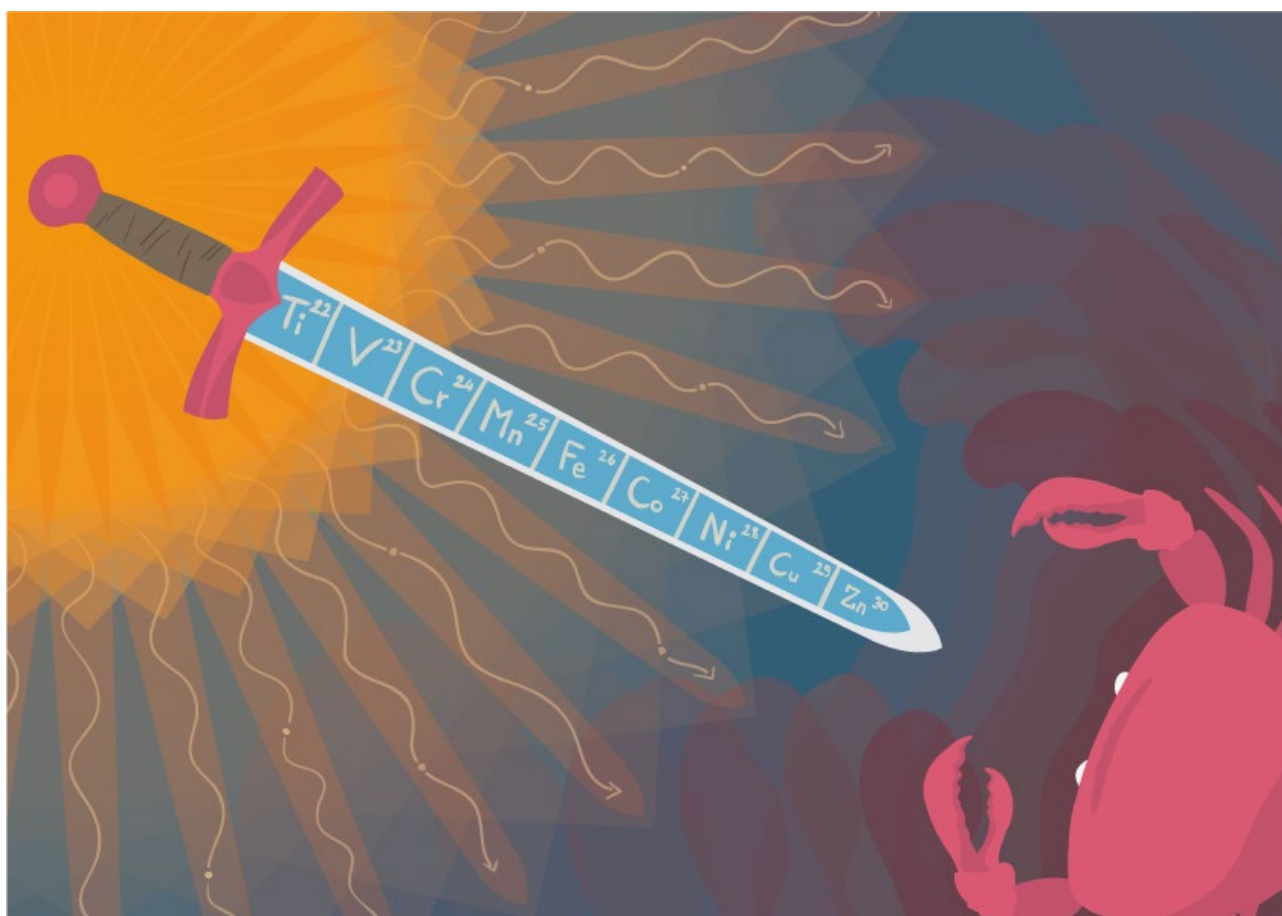
Lisa Gourdon,^a Kevin Cariou^{a,*} and Gilles Gasser^{a,*}

^a Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Laboratory for Inorganic Chemical Biology, 75005 Paris, France.

Abstract

Photodynamic therapy (PDT) and photoactivated chemotherapy (PACT) are therapeutic techniques based on a photosensitizer (PS) and light. These techniques allow the spatial and temporal control of the activation of drugs with light. Transition metal complexes are attractive compounds as photoactivatable prodrugs since their excited states can be appropriately designed by subtle modifications of the ligands, the metal centre, or the oxidation state. However, most metal-based PSs contain heavy metals such as Ru, Os, Ir, Pt or Au, which are expensive and non-earth-abundant, contrary to first-row transition metals. In this context, the exploration of the photochemical properties of complexes based on first-row transition metals appears to be extremely promising. This did encourage several groups to develop promising PSs based on these metals. This review presents up-to-date state-of-the-art information on first-row-transition metal complexes, from titanium to zinc in regard to their application as PSs for phototherapeutic applications.

KEYWORDS: Anticancer; Bioinorganic Chemistry; Medicinal inorganic Chemistry; Photoactivated Chemotherapy (PACT); Photodynamic Therapy (PDT); Transition Metal Complexes.



Biographies



Lisa Gourdon graduated from the Ecole Normale Supérieure (ENS) Paris and completed her MSc in biochemistry (PSL University) in 2020. Her first taste of scientific emulation came at the International Chemistry Olympiads that she attended in Vietnam in 2014. Since then, she has specialized in bioinorganic chemistry, particularly through internships in Clotilde Policar team (ENS Paris, France) and Ulrich Schatzschneider group (Würzburg University, Germany). She was awarded a ENS PhD scholarship to work under the supervision of Gilles Gasser and Kevin Cariou at Chimie ParisTech, on first-row transition metal complexes to perform intracellular photocatalysis for anticancer purposes.



Kevin Cariou received his PhD in 2006 from Sorbonne Université under the supervision of Max Malacria and Louis Fensterbank. From 2007 to 2009 he worked as a postdoctoral researcher in the group of Alison Frontier at the University of Rochester (NY, USA). He was appointed as CNRS Researcher in 2009 at the Institut de Chimie des Substances Naturelle in the team led by Robert Dodd. He obtained his HDR in 2015 and moved to Chimie ParisTech in 2020 and was appointed Director of Research in 2021. His interest lie in the development of synthetic methods to access biologically active molecules.



Gilles Gasser started his independent scientific career at the University of Zurich (Switzerland) in 2010 before moving to Chimie ParisTech, PSL University (Paris, France) in 2016 to take a PSL Chair of Excellence. Gilles was the recipient of several fellowships and awards including the Alfred Werner Award from the Swiss Chemical Society, an ERC Consolidator Grant, the European Biorganic Chemistry (EuroBIC) medal and the Pierre Fabre Award for therapeutic innovation from the French Société de Chimie Thérapeutique. Gilles' research interests lay in the use of metal complexes in different areas of medicinal and biological chemistry.

1 Introduction

Medicinal inorganic chemistry is a vibrant research field because of its incredible versatility.¹ The prototypical compound of this family is the anticancer drug cisplatin discovered more than 50 years ago by Rosenberg, which is activated by hydrolysis when entering the cell.² Since then, the interest in metal complexes in medicine has steadily increased. For example, other platinum drugs such as carboplatin³ or oxaliplatin⁴, and the arsenic-based drug As_2O_3 ⁵ have been developed and commercialized as anticancer therapeutic compounds.

However, these drugs act in a non-specific way, usually leading to heavy side effects. To avoid this problem, the use of an inactive prodrug, which can be specifically activated, is an efficient solution. To accomplish this, light can be used as an external stimulus, which will control the spatial and temporal activation of the drug.

Photodynamic therapy (PDT) is an approved technique based on a photosensitizer (PS), light and endogenous O_2 . The PS absorbs light to reach an excited singlet state. As the molecule returns to the ground state (GS), the energy can be dissipated in many ways. It can directly go back to the GS in a radiative way (by fluorescence) or in a non-radiative way (i.e., by generating heat). The molecule in its excited singlet state can also undergo intersystem crossing (ISC) to a different excited state, for example a triplet state. The triplet states have longer lifetimes than singlet ones (typically in the micro- to millisecond range vs the nanosecond range). Apart from relaxation to the GS – *via* a radiative or non-radiative pathway - this triplet state can initiate reactions with endogenous molecules in the cell. Currently, PDT has been classified into two types depending on the mechanism of action (Figure 1).

In type II PDT, the PS in its excited triplet state (^3PS) reacts with endogenous $^3\text{O}_2$ *via* energy transfer to produce highly reactive singlet oxygen $^1\text{O}_2$. There are two energy levels of $^1\text{O}_2$: $^1\Sigma_g$ and $^1\Delta_g$. A decay from $^1\Sigma_g$ can either lead to the GS or to $^1\Delta_g$. The latter is highly reactive and is responsible for the cytotoxicity of the PS. Type II PDT's efficiency can be characterized by two values: the lifetime of ^3PS (usually in the microsecond range) and by the singlet oxygen formation quantum yield Φ_Δ . This yield is defined as the ratio between the

number of singlet oxygen molecules formed and the number of photons absorbed. It can be more easily visualized as the fraction of triplet excited state complexes that is actually quenched by $^3\text{O}_2$.

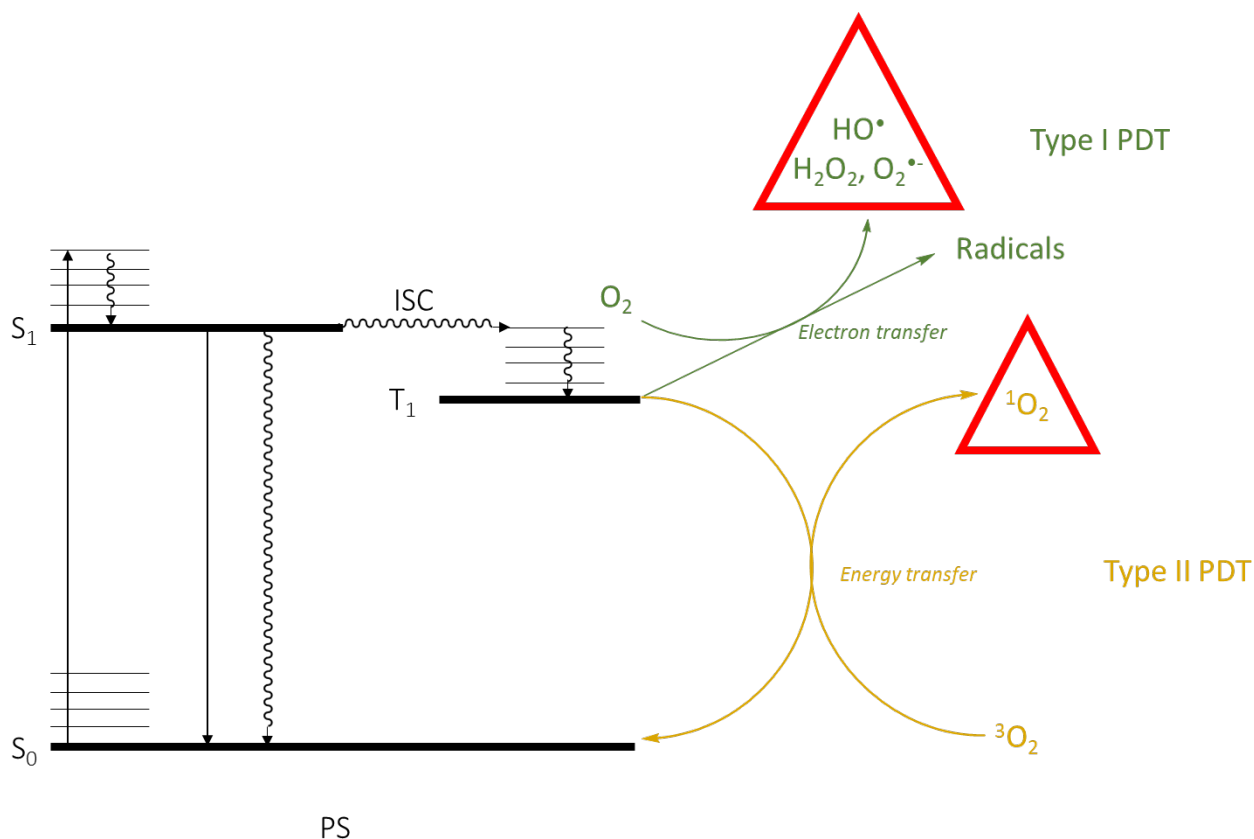


Figure 1: Jablonski diagram for generation of singlet oxygen. Nonradiative transitions are indicated by squiggly arrows while radiative ones are indicated by straight arrows. In black is represented the diagram of a typical metal complex with different spin multiplicities (for clarity, the GS is only represented as a singlet state, but might be a triplet state as well). In yellow is represented the energy transfer between T_1 and O_2 for type II PDT. In green is represented the electron transfer from T_1 leading to ROS for type I PDT.

Type I PDT, on the other hand, causes cell apoptosis *via* reactive oxygen species (ROS) such as hydroxyl or superoxide radicals. These ROS are produced *via* electron or hydrogen transfer from singlet or triplet excited states of the PS. Thanks to their tuneable redox properties, the use of metal complexes is particularly relevant for achieving type I PDT.

In PDT, the PS is eventually regenerated in its GS and not chemically modified during the process, it can therefore undergo many cycles of photon absorption and ROS production. The ideal metal-based PS should:

- Absorb in the visible range. Depending on the medical application, different wavelengths can be required. Red light allows for deeper tissue penetration, which can be sought after or avoided. For example, the Ru-based PS TLD1433, which is currently undergoing clinical trial against non-muscle

invasive bladder cancer (NMIBC), is activated with green light.⁶ The absorption range can be tuned by playing on the ligand coordination sphere.

- Possess a high quantum yield for $^1\text{O}_2$ generation.
- Have a rather long-lived triplet lifetime (in the microseconds range, for the molecule in its excited triplet state to diffuse to $^3\text{O}_2$ before relaxation to the GS) – by playing on the excited states of the metal centre.
- Be inactive in the dark.
- Be soluble in water and biological medium to penetrate cells and show binding affinity for the target (by intercalating DNA for example).

A related alternative to PDT is photoactivated chemotherapy (PACT), in which the photoactivated PS can lead to cell death *via* other mechanisms not involving O_2 .⁷ Since cancer cells are frequently hypoxic, the effectiveness of PDT may be limited by the low O_2 concentration in tumours. PACT can overcome this limitation as it relies on a prodrug, which, once photoactivated, can produce cytotoxic species, independently of the presence of O_2 . PACT agents do not regenerate after producing cytotoxic species, though; the drug is therefore stoichiometric and requires higher doses than for PDT, which acts in a catalytic manner. Due to the photochemical complexity of the PACT agents, it is not possible to establish a classification as clear for PDT. Sadler and co-workers, however, distinguished four main types of mechanisms in their recent minireview on the topic of PACT agents:⁸ photoinduced electron transfer, photosubstitution, bioactive ligand release, and ligand photocleavage. Some promising PACT agents have been developed, notably based on $\text{Pt}^{9,10}$ or Ru .^{11–13}

Several comprehensive reviews have recently covered metal-based PS for PDT,^{6,14–17} yet most of the examples presented were based on heavy and rare metals such as Pt, Ru, Ir, Re or Os. A recent review presented heavy-atom-free PS for PDT, focusing on boron-based and organic PS.¹⁸ In the present review, the focus will exclusively be on the use of first-row transition metals.

First-row transition metals are all more abundant on Earth than any metal from higher periods (Figure 2).¹⁹ From this point of view, the use of first-row transition metals for photoactivated anti-cancer therapy would be more sustainable compared to more rare heavy metals. Besides, many heavy metal complexes are toxic, even when not irradiated, and using first-row transition metal complexes could help reducing the prodrug's

dark toxicity. Moreover, five of these metals are essential to human health (i.e., Mn, Fe, Co, Cu and Zn). The use of these metals for drug design could therefore comfort pharmaceutical companies and patients who often associate heavy metal-containing complexes with toxicity.²⁰ It is important to highlight that such a statement is erroneous. As an example, grams of a gadolinium complex are given as a contrast agent to patients undergoing a magnetic resonance imaging (MRI) scan.²¹ One can also think that a mercury-containing complex, namely Thiomersal, is used as a preservative for vaccine.²²

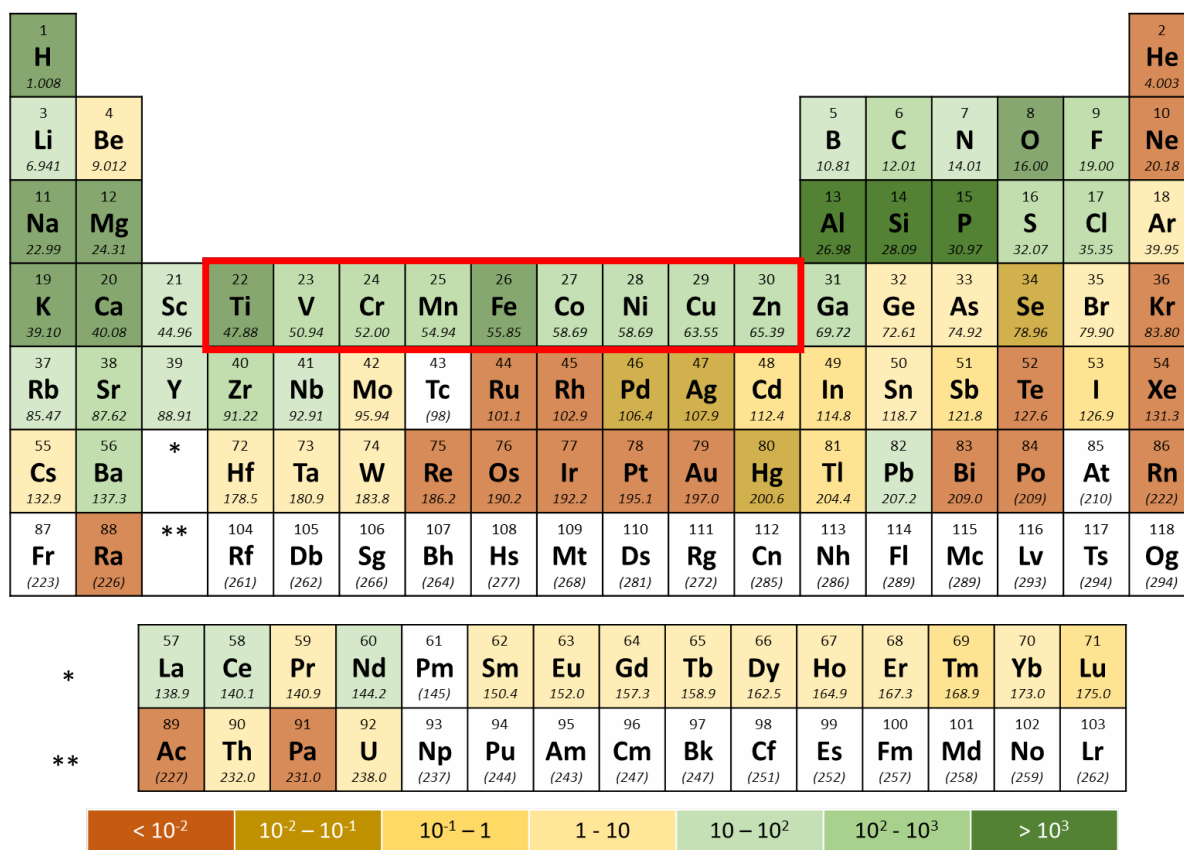


Figure 2: Abundance (in milligrams per kilogram of Earth's crust) of elements. First-row transition metals are more abundant than Ru, Os, Os, Ir or Au, commonly used in PDT.12 This review will present PS based on the metals framed in red.

A comprehensive mini-review from Behm and McIntosh gives a great perspective of the use, and associated challenges, of first-row transition metal complexes as PSs, although not specifically for applications in PDT or PACT,²³ which are the focus of the present review. First-row transition metals display characteristics that can prove challenging for photochemical endeavors.^{24,25} One can describe transitions in metal complexes as such: metal-centred (MC) for d-d transitions, ligand-centred (LC) for transitions between occupied (π) and

unoccupied (π^*) ligand orbitals, metal-to-ligand and ligand-to-metal charge transfers (MLCT and LMCT, respectively) when both metal and ligand orbitals are involved (Figure 3).

The ligand field of first-row metal complexes (i.e, the energy difference between t_{2g} and e_g levels of the d orbitals) is generally low in terms of energy. This means that MC transitions are favourable; the resulting MC state is generally distorted, low in energy, and therefore short-lived because it is subject to non-radiative deactivation towards the GS.²⁴ One way to circumvent this problem is to use filled d subshells - in Ni(0), Cu(I) or Zn(II) complexes, therefore eliminating MC transitions and favouring MLCT absorption in the visible range. Otherwise, for $3d^1$ - $3d^9$ complexes, the d orbitals can be destabilized by σ -donor ligands, increasing the d-d orbital splitting. However, when MC states are lower in energy than the charge transfer, complexes are labile, because the overlap between metal orbitals and ligand ones is weak.²⁵ This means that ligand exchange or release are favoured, which can be desirable in PACT agents, but can also leads to stability issues, particularly in biological media. The MC bands can also be quenched by oxidation of DNA guanine bases, which causes fatal DNA damage. To achieve MLCT absorption instead of MC absorption, the use of π -accepting ligands is another solution. Finally, increasing the rigidity of the complex usually prevents conformational reorganization of the complex that could lead to non-radiative deactivation.

In addition to this, since the d-orbital splitting is small for first-row transition metals, the complexes can have either a high spin or low-spin multiplicity in the GS – depending on the position of the ligand in the spectrochemical series. The photochemistry of 1st row metal complexes is therefore significantly more complex than the simplified Jablonski diagram depicted PS in Figure 1, because these complexes could be attaining metal-centred excited states that are not just singlets but triplets as well.

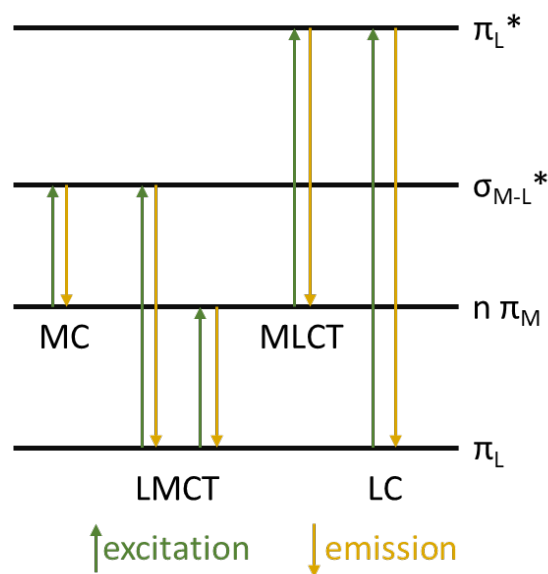


Figure 3: Electronic transitions (excitation and emission) between frontier molecular orbitals for a typical 3d complex with $ML_6 O_h$ symmetry (without π -bonding). π_L and π_L^* are the non-bonding π orbitals of the ligand, σ_{M-L} the σ -bonding metal-ligand orbital and $n \pi_M$ the non-bonding π metal orbital. Adapted from ref ²⁴.

Furthermore, in 3d transition metals, spin-dependent relativist effects such as spin-orbit coupling are not so significant compared to 4d or 5d metal complexes.²⁶ Because of the weakness of spin-orbit coupling, triplet excited states are more difficult to access *via* ISC, contrary to heavy metals. This feature can be overcome by choosing rigid ligands such as porphyrins, which usually lower the splitting between the singlet and triplet excited states. That said, the weak spin-orbit coupling in 1st row transition metals makes the Russel-Saunders approximation reasonable: we can hence consider the 3PS to 1GS transition as spin-forbidden, allowing the 3PS state to be rather long-lived – even though there are still possible nonradiative processes that are difficult to suppress. This feature combined to low-lying 3PS excited states allow favourable energy transfer to 1O_2 , and therefore a high Φ_Δ . The photochemistry of first-row transition metal complexes, although challenging, is promising, and allows designing inexpensive and sustainable anticancer drugs and the purpose of this review is to discuss the advances in this promising field of research. This review will be restricted to articles discussing phototoxic complexes, which have been tested on cells. We have decided to also mention in the review the articles which describe compounds which were inefficient in cells to show the difficulty to obtain such phototoxic compounds based on 1st row transition metals. We chose to exclude nanoparticles from the scope of this review to focus our attention only on molecular complexes. We have organized this manuscript

with one section by element, inside which the compounds are listed to provide an overview of promising phototoxic complexes and their mechanisms of action.

2 Phototoxic first-row transition metal complexes

2.1 Titanium

Due to its $[Ar]3d^24s^2$ electronic configuration, titanium mainly exists in its +4 oxidation state. Ti(IV) complexes were explored as anticancer drugs, but their tendency to quickly hydrolyse and form aggregates in cells hindered further research.²⁷ To the best of our knowledge, despite a few attempts to design titanium (IV) phthalocyanines suitable for PDT,^{28–30} no titanium complex showed any phototoxic behaviour. However, TiO₂ nanoparticles display an anticancer effect under UV-A irradiation : several reviews already treated the subject.^{31–33}

2.2 Vanadium

Vanadium is an essential trace element that is present in all mammalian tissues.³⁴ High oxidation states of vanadium (+4 and +5) can be stabilized by the well-known oxo ligand, owing to its π -donating ability. Oxovanadium(V) and peroxovanadium(V) complexes acting as ¹O₂-mediated DNA cleavers under UV-A light were described, but they are not active in visible light because of their predominant LMCT absorption in the UV range.^{35–37} In vanadium(IV) complexes however, visible-light absorption can be achieved. The 3d¹ electronic configuration in these one-electron paramagnetic complexes allows for a near-IR d-d band. Usually, a ligand-centred (LC) band can be present in addition to the MC one. Moreover, oxovanadium(IV) complexes were extensively studied, particularly by Chakravarty and co-workers.^{38–54} More specifically, in 2007, they presented oxovanadium(IV) complexes with *N,N*-donor heterocyclic base, such as dipyrrophenazine (dppz), showing a weak d-d band around at 840 and 700 nm and another one around 470 nm (**V-1**, Figure 4, the dppz ligand is highlighted in light pink).⁵¹ These complexes bind to calf thymus DNA and cleave it under irradiation with UV-A light and red light, both *via* a ¹O₂ pathway. In 2010, the same team

published a promising oxovanadium(IV) complex capable of intercalating DNA and cleaving it under red light irradiation (>750 nm) *via* a hydroxyl radical pathway this time. These compounds have been studied on HeLa cells and displayed an IC₅₀ of 12.0 μM in visible light (400-700 nm) vs >100 μM in the dark (**V-2**).⁴⁹ This complex also displayed a PDT effect under UV light activation (1 μM in HeLa cells under 365 nm), by forming ¹O₂ and HO[•], thus cleaving DNA, bovine serum albumin (BSA) and lysozyme. This is due to the presence of both a weak d-d band around 715 nm in 15% DMF-Tris-HCl buffer and a n-π* transition around 350 nm in the dipyrrophenazine ligand. This type of quinoxaline derivatives possesses excited triplet states – ³(n→π*) and ³(π→π*) that are known to cleave DNA *via* electron transfer.⁵⁵ In 2012, the same authors reported oxovanadium(IV) complexes bearing polypyridyl ligand with the same dppz base cleaving calf thymus DNA at 705 and 785 nm *via* a HO[•]-mediated pathway, thanks again to the vanadium-centred d-d band.⁴⁵ Promising IC₅₀ values of 3.9 μM in HeLa cells under visible light irradiation were obtained while a low toxicity in the dark (IC₅₀ = 40 μM) was observed.

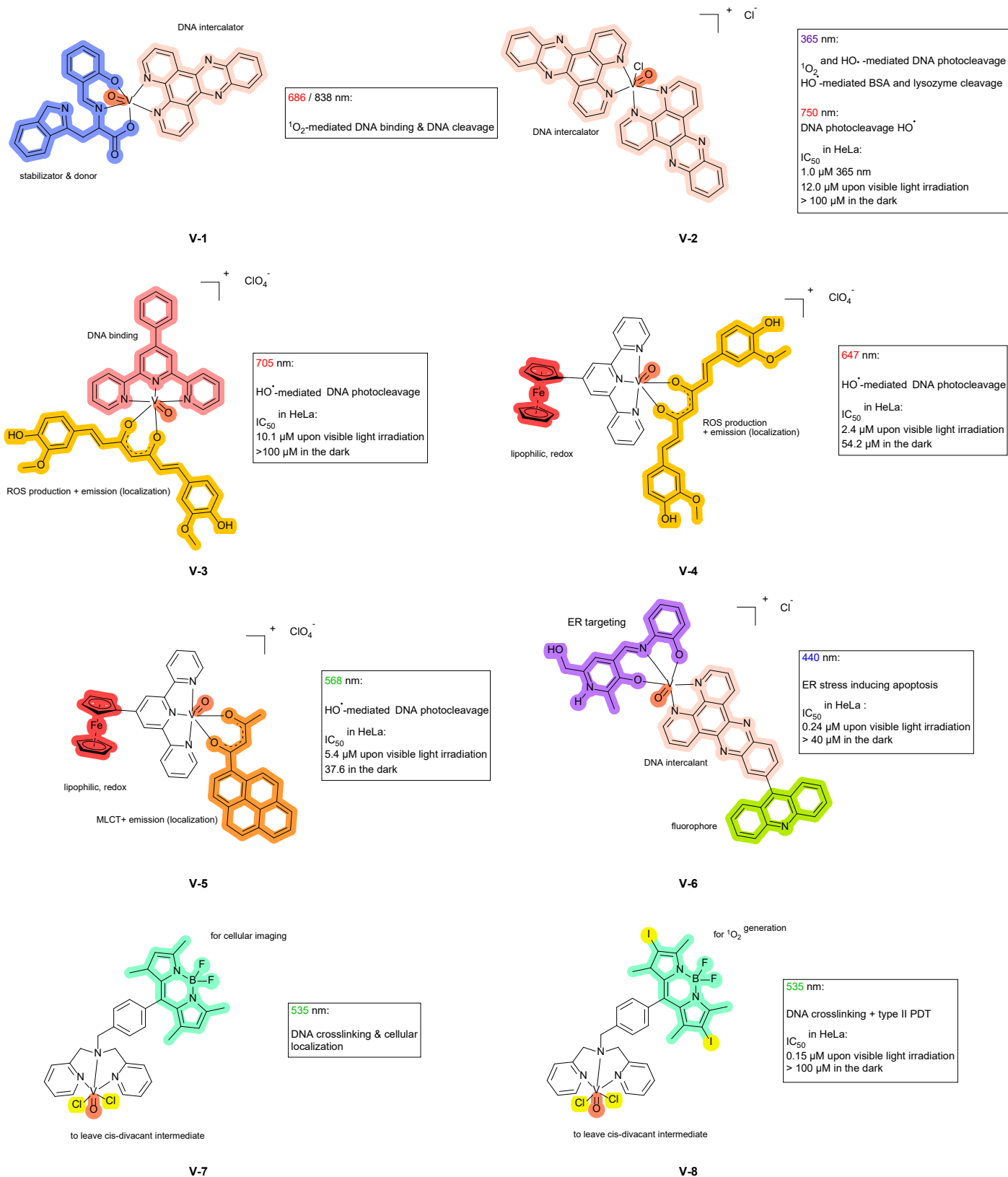


Figure 4: Oxovanadium(IV) complexes developed for PDT applications. In this figure are indicated: the absorption maximum or maxima (coloured if in the visible range), the mechanism responsible for the cell's death, the IC₅₀ values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

Curcumin (yellow moiety in **V-3** and **V-4**) has been expansively investigated as a therapeutic agent against various diseases, including cancer.⁵⁶ From this perspective, oxovanadium(IV) complexes of curcumin and terpyridine (highlighted in dark pink) – for ROS production and DNA binding, respectively – were synthesized by Chakravarty and co-workers in 2014 (**V-3**).⁵⁷ Since curcumin is green-emissive, cellular imaging could be performed. A derivative containing a triphenylphosphonium moiety allowed mitochondrial localization. The complex absorbs thanks to its curcumin $\pi \rightarrow \pi^*$ band around 450 nm and its MC band around 720 nm and shows good type I PDT effect under these wavelengths with IC_{50} of 10 μ M in visible light vs >100 μ M in the dark (in HeLa cells). Another promising phototoxic oxovanadium(IV) agent with a curcuminoid ligand was reported in 2014 (**V-4**).⁴³ This complex contains a ferrocene-terpyridine ligand. The ferrocene (highlighted in red) is non-toxic, and lipophilic, which should increase the cellular uptake of the resulting complex. The redox properties of the ferrocene also clearly improved the PDT effect of the molecule: the ferrocene can be photooxidated into a ferrocenium Fc^+ that undergoes a Fenton type reaction with the metal centre, which initiates the formation of HO^\bullet radicals.⁵⁸ The complex displays different absorption bands: around 414-436 nm because of the $\pi \rightarrow \pi^*$ transitions in the curcuminoid ligand; around 585 nm for the MLCT. The latter is strong and only present if the Fc moiety is attached to the terpyridine, as if it is replaced by a phenyl only a weak d-d band around 777 nm was measured. The complex binds strongly to calf thymus DNA and can cleave plasmid DNA under blue and red light by formation of hydroxy radicals. This leads to cell's death *via* an apoptosis pathway, with good phototoxicity results. Cellular localization of the complex was also achieved thanks to the emissive properties of the curcuminoid derivatives. An analogue of this complex where the curcumin is replaced by a pyrene moiety was also synthesized (**V-5**).⁴¹ This compound is also an avid DNA binder and cleaves plasmid DNA under green light *via* a type I PDT pathway. Interestingly, the complex is quite phototoxic on HeLa and MCF-7 cancer cells but shows no toxicity – even under irradiation – on 3T3 non-cancerous cells.

An interesting target for chemotherapeutic agents is the endoplasmic reticulum (ER) as it plays a central role in the folding of essential proteins. ER stress – by ROS for example – could induce apoptosis. As vitamin B6

(VB6) targets the ER, complex **V-6** bearing a ligand derived from VB6 (highlighted in purple) and a dppz)derivative (acting as a PS) appended with an acridinyl moiety (as a fluorophore, in bright green) was developed.⁵⁹ The VB6 group was previously demonstrated to enhance cancer cell uptake as tumours are highly VB6-demanding, which enters the cells *via* a VB6 transporting membrane carrier.⁶⁰

Chakravarty and co-workers most recent work was focused on BODIPY-appended cis-dichloro-oxovanadium(IV) complexes (**V-7** & **V-8**).^{38,52} The *cis* disposition of the chlorides allows for DNA crosslinking, making the drug a transcription inhibitor, similarly as cisplatin. The first chloride is labile, but the second one can only be hydrolysed under light irradiation, which makes the DNA crosslinking temporally and spatially controllable. The BODIPY (green moiety in **V-7** and **V-8**) is responsible for an additional mode of action, based on light. The frontier molecular orbitals of BODIPY are at the origin of the 500 nm absorption bands and leads to generation of ¹O₂ with a quantum yield of approximately 0.6 in DMSO, causing apoptosis *via* a type-II PDT pathway upon red light (633 nm) irradiation.³⁸ A diiodo derivative (**V-8**) gave better PDT results than complex **V-7** as it is non-emissive. These heavy atoms favoured spin-orbit coupling, and thus inter-system crossing. **V-8** therefore generates significantly more ¹O₂ than **V-7**, which is more emissive. Thanks to the BODIPY moiety, emission properties of the complexes allowed cellular imaging: the complex localized in the mitochondria. That kind of complex is unique as it acts both as a transcription inhibitor and a ¹O₂-mediated PS.

2.3 Chromium

Although some chromium complexes possessing high ¹O₂ quantum yields have been reported,^{61,62} their phototoxic activities are generally rather disappointing. The biological study of a Cr(III) complex which was expected to be very promising as a PDT PS was reported in 2019 by the Heinze and Gasser groups (**Cr-1**, Figure 5).⁶¹ This complex is photostable, water-soluble, and displays a good ¹O₂ quantum yield (61 %) in DMF. Singlet oxygen is produced by energy transfer from the doublet excited state of the Cr(III) compound with ³O₂. The phototoxicity was evaluated in cells: while remaining essentially non-toxic in the dark, the cytotoxicity under 450 nm irradiation was increased by 5-fold. This rather disappointing PDT effect was

attributed by the author to a poor cell uptake, although the presence of various biomolecules in cells that could prematurely quench the excited state and preclude its reaction with singlet oxygen could be another plausible explanation.

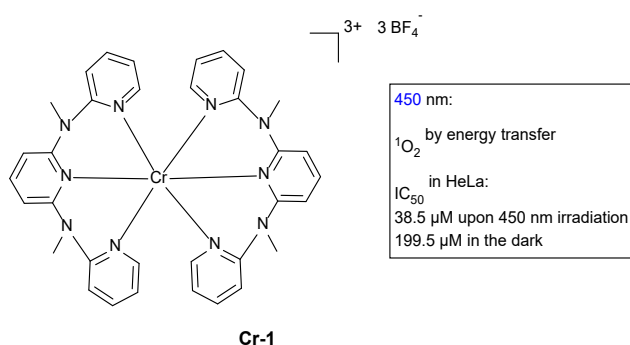


Figure 5: Chromium complex displaying phototoxicity. In this figure are indicated: the absorption maximum, the mechanism responsible for the cell's death, the IC_{50} values upon irradiation and in the dark (and the cell line in which they have been measured).

In summary, at this stage, chromium does not seem to be suitable for the design of PDT agents. Very importantly, one has also to consider that chromium is not entirely stable in its +3 oxidation state under biological conditions,⁶³ as a 2016 study showed that Cr(III) compounds found in dietary supplements can be oxidized *in cellulo*,⁶⁴ leading to extremely carcinogenic Cr(VI) species.⁶⁵

2.4 Manganese

Manganese is a very abundant metal and is essential for humans as it is present in hydrolases, superoxide dismutase, and photosystem II. Apart from manganese oxide particles, very few manganese-based compounds have shown phototoxic properties. Nevertheless, we can cite the work of Liu and co-workers on Mn(III) (and Fe(III)) mesotetrakis(carboxyl)porphyrins (**Mn-1**).⁶⁶ The porphyrin **Mn-1** displayed promising phototoxicity results in Hep G2 cells (19.0 μM upon 625 nm irradiation while remaining non-toxic in the dark up to 100 μM), acting *via* a hydroxyl radical pathway. Moreover, several potential Mn tricarbonyl-based PACT agents have been developed, to act as photo-CORMs (carbon monoxide-releasing molecules). Although most photo-CORMs were developed to release CO as a signal molecule, some highly active photo-CORMs led to cell death under irradiation. Schatzschneider and co-workers worked on a photo-CORM showing phototoxicity under UV light thanks to CO release (**Mn-2**, Figure 6).⁶⁷ The cell biomass of HT29 cells was

significantly reduced (up to about 30%) with 20 μM of **Mn-1** upon UV light irradiation, while remaining constant in the dark up to 100 μM . Mascharak and co-workers also reported a Mn-based photo-CORM capable of eradicating human colorectal adenocarcinoma cells in a dose-dependent manner (while remaining non-toxic in the dark up to 100 μM).⁶⁸ This complex also did not show any toxicity – even upon irradiation – on human embryonic kidney cells (HEK-293). An analogue showing a red-shifted absorption and meaningful phototoxicity results was recently developed (**Mn-3**).⁶⁹ The introduction of a conjugated quinoline ring (in grey) allowed the complex to absorb green light (525 nm). Manimaran and co-workers worked on Mn(I) (and Re(I)) crown ether photoCORMs that induce apoptosis in different cancer cell lines upon irradiation at 365 nm, with IC_{50} values of 7.15 μM in HCT-15 cells for example, vs > 50 μM in the dark (**Mn-4**).⁷⁰

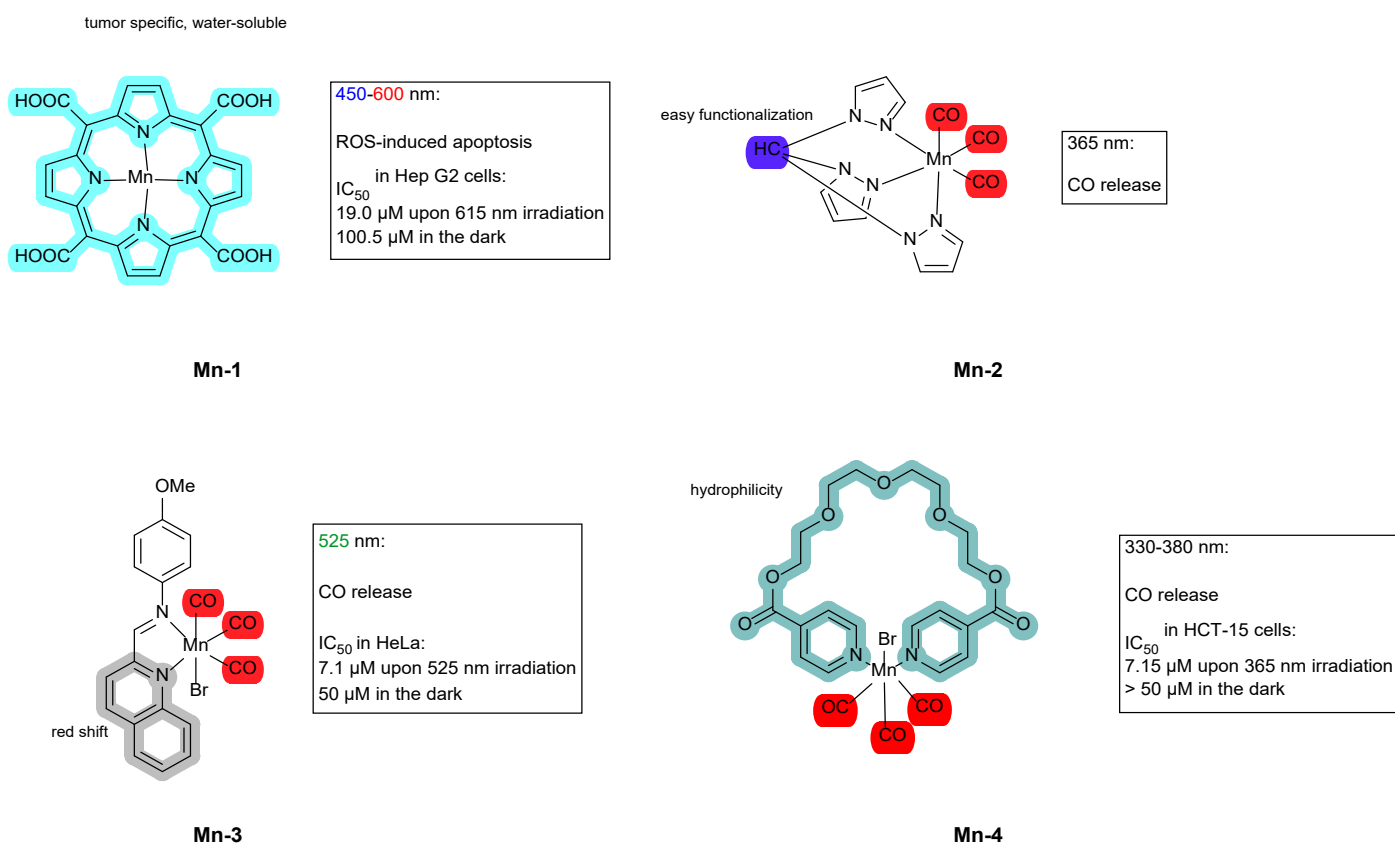


Figure 6: Mn-based photoCORMs. In this figure are indicated: the absorption maximum or maxima (coloured if in the visible range), the mechanism responsible for the cell's death, the IC_{50} values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest.

Overall, if promising Mn-based photoCORMs have been successfully designed, efficient PDT PSs are still lacking. Yet, article study presenting Mn(I) complexes with long enough LMCTs suitable for triplet-triplet energy transfers was recently published, which gives hope for the design of type II PDT agents.⁷¹

2.5 Iron

Iron is the most abundant transition metal in the Earth's crust and is widely present in the human body (for the most part in haemoglobin, which accounts for more than half of the 4 to 5 grams of total body iron). The use of this metal in drugs is therefore not only more affordable but also particularly reassuring for patients and companies. The commercialized anticancer drug bleomycin (a nonribosomal peptide) acts as a chelator of endogenous metals, particularly iron.⁷² The complex thus formed cleaves DNA by generating hydroxyl radicals (in the dark). This mode of action drew attention to iron complexes for therapeutic purposes. For example, the iron-containing compounds ferroquine and ferrocifens are undergoing pre-clinical trials as antimalarial and anticancer drugs, respectively.⁵⁸ In addition, iron is the lighter congener of ruthenium, which is present in many PDT PSs. However, iron possesses low-energy MC states that are therefore very short-lived, which makes oxygen sensitization, as well as the charge transfer to ligands, less favourable. To overcome this issue, the use of σ -donor or π -accepting ligands, as well as rigid structures can help achieve longer ³MLCT lifetimes.⁷³ For a more detailed analysis, we highly recommend the review by Wenger and co-workers which describes the challenges associated with iron comparatively to ruthenium.⁷⁴

Although a wide variety of iron oxidation states can exist in complexes – from Fe(0) to Fe(VI) –, the ferrous (+2) and ferric (+3) states are mostly used. In 2010, Roelfes and co-workers discovered that the cytotoxicity of their Fe(II) complex was significantly enhanced under UV irradiation.⁷⁵ Double-strand DNA cleavage was observed *via* both hydroxyl radical and singlet oxygen pathways. Since then, Chakravarty and co-workers studied Fe(II) complexes as PDT agents. They designed diamagnetic complex **Fe-1** with a 3d⁶ configuration, photocleaving DNA by generating O₂^{•-} and HO[•] radicals under green light (Figure 7). The complex bears a terpyridine moiety (in purple), which acts as a PS, a DNA binder, and a stabilizer of the ferrous state. The terpyridine being a π -acceptor moiety, an MLCT band (from the metal centre to the ligand) is observed

around 565 nm, as well as an LC band in the UV region. Terpyridines are also emissive; however, when coordinated, the fluorescence is mostly quenched thanks to the low-lying d-d orbitals of the metal. The weak luminescence of the complex still allowed cellular imaging, which revealed that the complex accumulates in the nucleus, where it binds in a partial intercalative mode to DNA. The same team published another diamagnetic Fe(II) complex bearing polypyridyl ligands, which induces apoptosis in cancer cells with significant phototoxicity under visible light (**Fe-2**).⁷⁶ A new type of Fe(II) complex was presented in 2018 by Tabrizi: it bears a tridentate ligand (which stabilizes the ferrous state as a pincer) appended with a BODIPY moiety known for its mitochondria-targeting, photodynamic and emissive properties (**Fe-3**).⁷⁷ The complex displays good cytotoxicity upon 500 nm irradiation (1.06 μ M in HeLa cells) while remaining essentially non-toxic in the dark. The BODIPY allowed cellular imaging: the complex actually accumulates in the mitochondria.

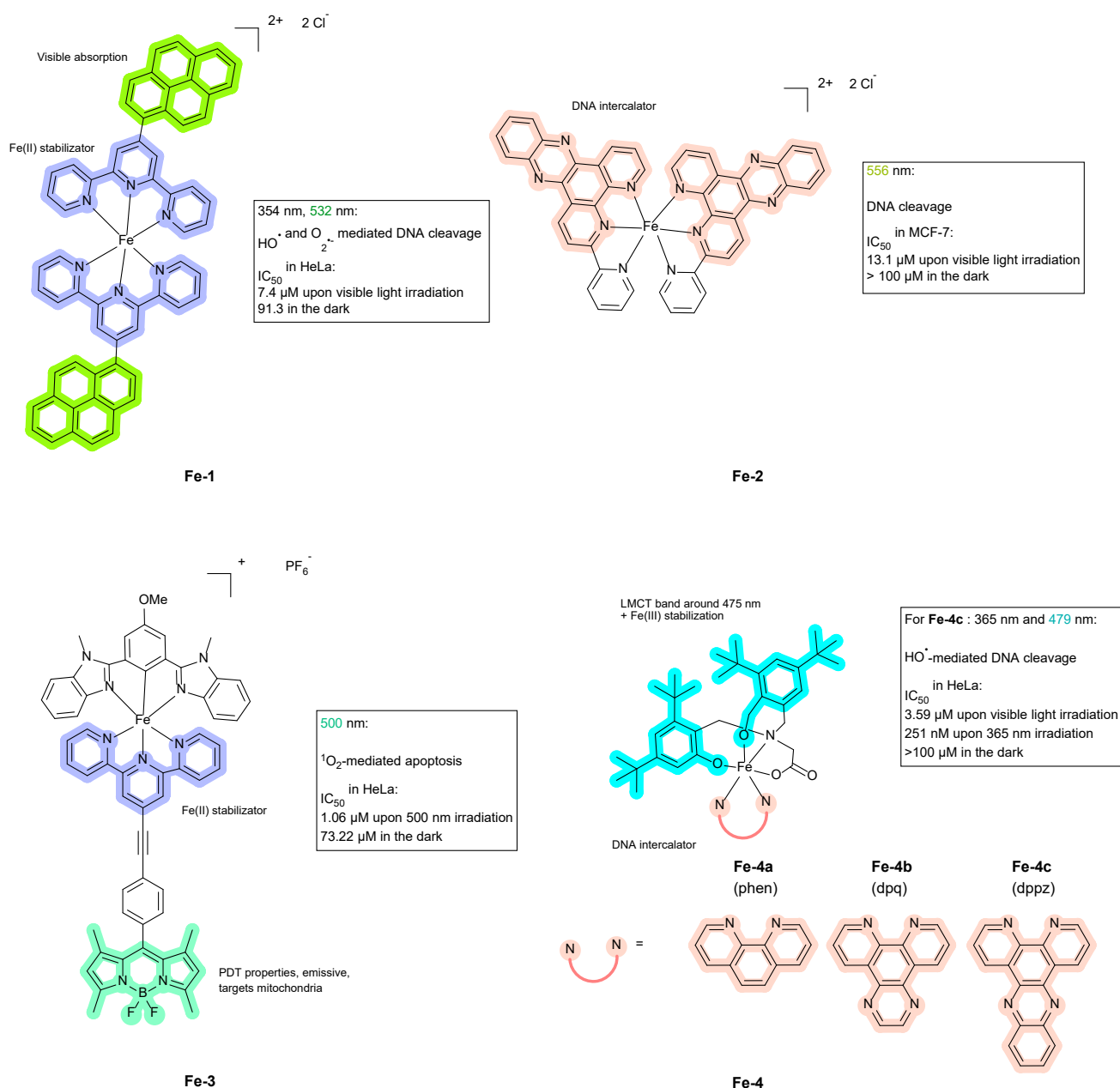


Figure 7: Iron complexes displaying phototoxicity. In this figure are indicated: the absorption maximum or maxima (coloured if in the visible range), the mechanism responsible for the cell's death, the IC₅₀ values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

Contrary to Fe(II) complexes, Fe(III) are prone to reduction by glutathione *in cellulo*, which drastically alters their stability. This result led several teams to focus on ferric complexes rather than ferrous ones.⁷⁸ With this in mind, a series of iron(III) complexes bearing a bis-phenolate (for low-energy charge transfer to the metal) and a modified dppz base (for DNA binding) were reported and displayed good phototoxicity upon visible

irradiation and sub-micromolar toxicity in the UV range, with minor dark toxicity (**Fe-4** complexes).^{78,79} These $3d^5$ high spin compounds are redox active and act by generating hydroxyl radicals by electron transfer, leading to cancer cell death by apoptosis. **Fe-4** complexes contain lipophilic tertiary butyl groups for lipophilicity and – again – dppz moiety derivatives for intercalative properties (particularly the dppz derivative **Fe-4c**). The tetradentate structure of the ligand (with two phenolates, one amine, one acetate) stabilizes the Fe(III) against reduction by glutathione. The **Fe-4** complexes absorb intensely in the UV region because of the N-N moiety, whereas the phenolate-to-Fe(III) charge transfer is responsible for the broad absorption around 475 nm. The absorption tail goes up to higher wavelengths, cytotoxicity could therefore be evaluated under red light. The compounds cleave DNA *via* a hydroxyl radical pathway, particularly under UV irradiation, but also upon visible irradiation. Another phototoxic Fe(III) complex was presented in 2012 (**Fe-5**, Figure 8):⁸⁰ it partially intercalates DNA and damages it upon near-IR light irradiation. This absorption at exceptionally high wavelengths was achieved thanks to the LMCT from the π frontier molecular orbital of a catecholate ligand to the Fe(III) centre, around 805 nm. The complex also bears an anthracenyl moiety which acts as a DNA binder and a fluorophore. HeLa and MCF-7 cancer cells die in an apoptotic pathway because of HO^\bullet radicals. Another catecholate Fe(III) complex was designed with a triphenylphosphonium moiety, allowing mitochondria targeting thanks to its positive charge.⁸¹

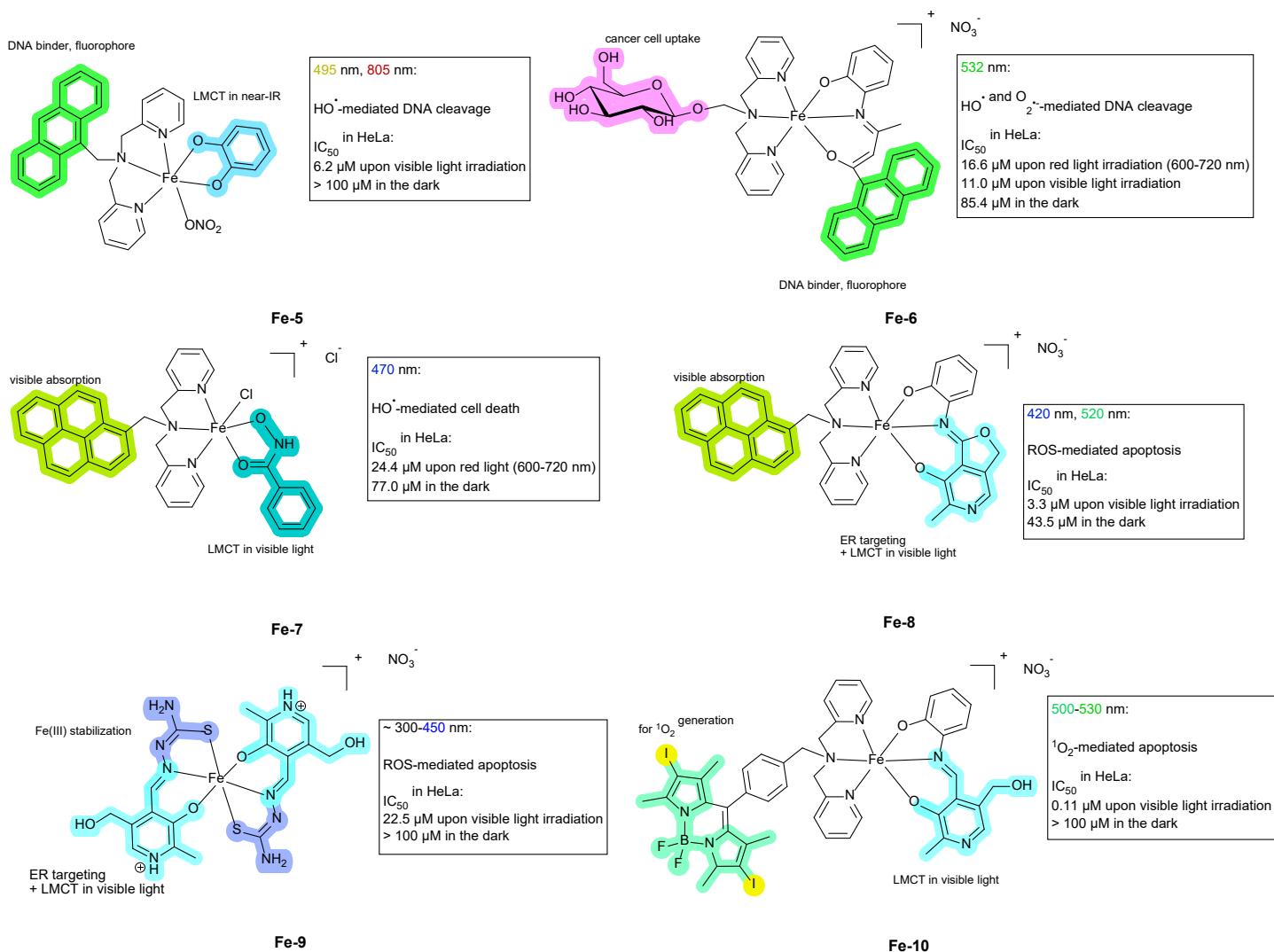


Figure 8: Iron complexes displaying phototoxicity. In this figure are indicated: the absorption maximum or maxima (coloured if in the visible range), the mechanism responsible for the cell's death, the IC₅₀ values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

In 2014, a phototoxic glucose-appended Fe(III) complex was designed (**Fe-6**).⁸² In tumours, the glucose transporter GLUT-1 is overexpressed, therefore, the addition of a carbohydrate could specifically improve the cellular uptake in cancer cells.⁸³ The phenolate-to-Fe(III) CT band displays a shoulder around 500 nm and the absorption tail goes up to 700 nm, which allows a PDT effect under red light irradiation. The reported high-spin complex cleaves DNA *via* a type I PDT pathway, which induces cell's apoptosis.

The same year, an article on Fe(III) benzhydroxamates of dipicolylamines (**Fe-7**) was published.⁸⁴ **Fe-7** exhibits phototoxicity on HeLa cells under visible light (14.6 μM) while remaining essentially non-toxic in the dark (77.0 μM). The compound displays a broad and intense absorption band – attributable to a

benzhydroxamate-to-Fe(III) charge transfer – with an absorption tail going up to 650 nm, which allowed the authors to study the phototoxicity upon red light (24.4 μM).

Similarly to the oxovanadium(IV) complex previously described (see **V-6**, Figure 4), Fe(III) complexes bearing a ligand based on VB6 (in light blue) for ER targeting (and visible absorption thanks to the LMCT band) were designed by Chakravarty and co-workers (**Fe-8**).⁸⁵ Interestingly, these complexes particularly accumulate in cancer cells and induce cell death by ROS-based ER stress, while being 5 to 6 less toxic in normal cells. Other VB6-based complexes were designed,⁸⁶ with thiosemicarbazones as tridentate donor ligands and DNA binders (**Fe-9**).⁸⁷ Lysosome selective phototoxicity was observed on a Fe(III) complex with a VB6 Schiff base bearing a diiodinated BODIPY for singlet oxygen generation (**Fe-10**).⁸⁸ This complex was especially cytotoxic in HeLa cells upon visible light irradiation (0.11 μM vs > 100 μM in the dark), inducing apoptosis *via* a type-I PDT pathway. Unfortunately, no *in vivo* studies have been conducted, avoiding a full assessment of the potential of this compound.

Curcumin complexes of Fe(III) were published in 2021 (**Fe-11**, Figure 9).⁸⁹ Cancer cells over-express nutrient receptors such as biotin receptors, which explains why the complex appended with biotin (in pink, **Fe-11a**) displays better uptake and higher phototoxicity on various cancer cell lines than the one without biotin (**Fe-11b**). Thanks to the curcumin ligand, **Fe-11** complexes generate hydroxyl radicals upon irradiation, hence causing cell apoptosis. The Fe(III) mesotetrakis(carboxyl)porphyrin analogue of **Mn-1** displayed disappointing phototoxicity results on Hep G2 cells (137.5 μM upon irradiation vs 175.5 μM in the dark), which highlights the considerable influence of the metal centre on the complexes photochemotherapeutic properties.⁶⁶ In 2020, Fe(II) polypyridine complexes with extension of the π -system were designed to achieve red-shifted absorption into the biological spectral window (600 – 900 nm).⁹⁰ However, the complexes were poor singlet oxygen generators and only displayed a slight cytotoxicity enhancement upon exposure with 480 and 540 nm light in HeLa cells. Although not as well developed as for manganese, phototoxic iron-based photoCORMs have also been studied.^{91,92}

Oxo-bridged diiron(III) complexes were shown to be photoactive thanks to intense oxo \rightarrow Fe(III) charge transfer. Recently developed oxo-bridged diiron(III) complexes displayed tumour-specific anticancer activity thanks to HO \cdot -mediated DNA cleavage (**Fe-12**).⁹³ Another Fe(III) oxo-bridged complex with salen ligands showed good phototoxicity results on various cancer cell lines (**Fe-13**).⁹⁴ The salen ligand allows for an LMCT band between 400 and 600 nm, which makes photoexcitation with red light possible. The charge separated excited species induces the production of O $_2^{\cdot-}$ and hence hydroxyl radicals, causing fatal DNA damage.

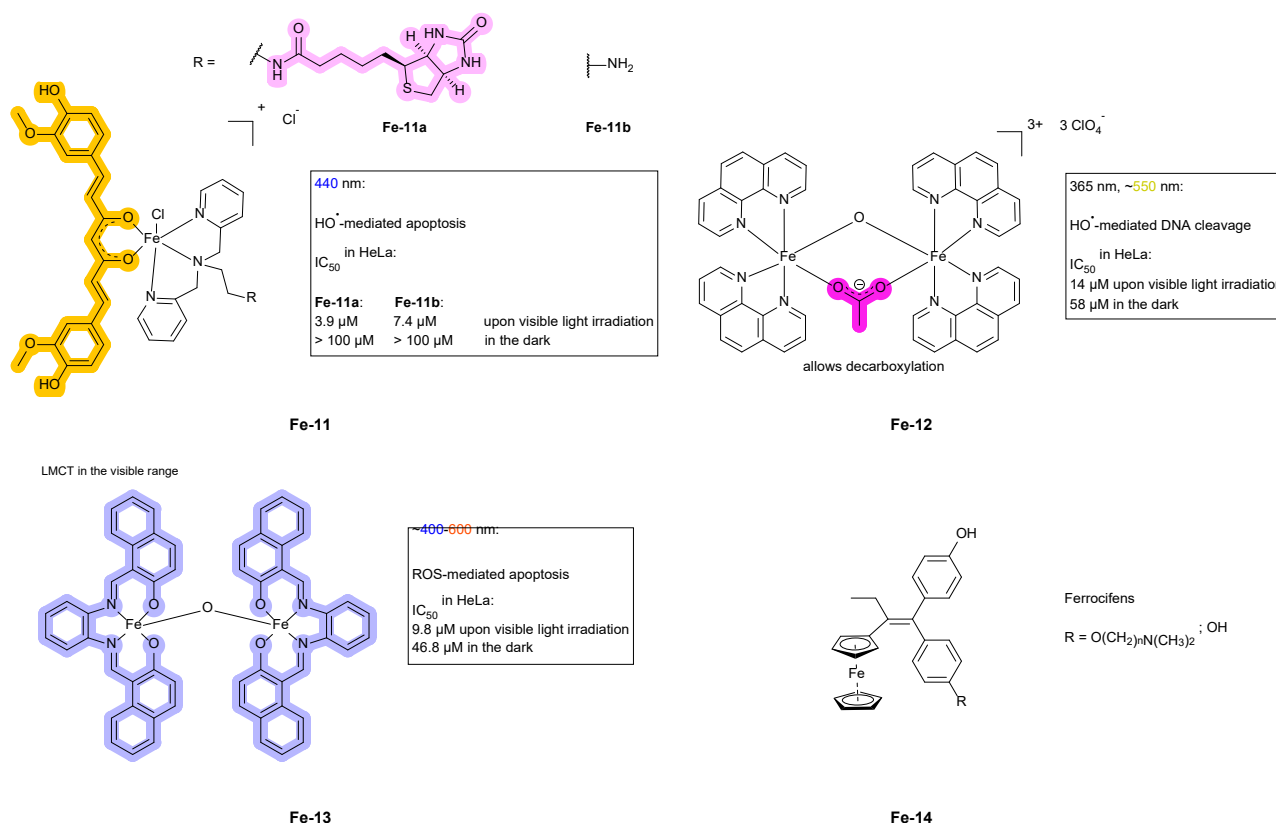


Figure 9: Iron complexes displaying phototoxicity. In this figure are indicated: the absorption maximum or maxima (coloured if in the visible range), the mechanism responsible for the cell's death, the IC $_{50}$ values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

We take advantage of this section on iron to recall the undeniable interest of the ferrocene group in the design of (photo)therapeutic drugs. As previously described (See Figure 4), ferrocene has attracted attention due to its low toxicity, lipophilicity and favourable redox properties allowing the formation of hydroxyl radicals.^{58,95} Ferrocifens (ferrocene derivatives of 4-hydroxytamoxifen, **Fe-14**), for example, have been extensively studied as chemotherapeutic agents against breast cancers.⁹⁶ Chakravarty and co-workers

published a study on different ferrocenyl terpyridine 3d metal complexes conjugates, based on Fe(II), Co(II), Cu(II) and Zn(II) ions.⁹⁷ The Fe(II) ferrocenyl complex did not show any toxicity in HeLa cells up to 50 μ M, both upon irradiation and in the dark, despite promising photocleavage activity.

2.6 Cobalt

Cobalt is of great interest, as an essential element present in various metalloproteins and cobalamin – also known as Vitamin B₁₂. Cobalt complexes showed promising photo-properties or DNA-cleaving activity, similarly to Ru. Phototoxic Co(III) complexes were extensively studied. For example, a Co(III) DNA-intercalating complex, active under 365 nm irradiation, was reported (**Co-1**, Figure 10).⁹⁸ Photoexcitation of a charge-transfer band around 400 nm induces the production of singlet oxygen and leads to DNA cleavage *in vitro*. To confirm the type-II PDT mechanism hypothesis, a strand scission experiment was carried out in D₂O. Singlet oxygen has a longer lifetime in D₂O than in H₂O,⁹⁹ and greater photocleavage was indeed observed in D₂O. Phototoxic curcumin-releasing cobalt complexes were studied as promising PACT agents.¹⁰⁰ These complexes release curcumin when the Co(III) centre is reduced into Co(II), which is of great interest since reducing conditions are typically found in tumours. Chakravarty and co-workers studied Co(III) complexes releasing curcumin and mitocurcumin (a dicationic bis-triphenylphosphonium derivative of curcumin, highlighted in yellow in **Co-2**) *via* photoreduction under 420 nm irradiation.¹⁰⁰ The mitocurcumin found in **Co-2** complex augments the cellular uptake thanks to its +2 charge. Other curcumin-releasing complexes were developed by Hambley and co-workers (**Co-3**): they demonstrated that the Co(III) centre can be reduced either by biological reductants or upon irradiation.¹⁰¹ These Co(III) chaperone complexes of curcumin were very effective upon visible light irradiation, both in oxygenated and hypoxic conditions. Interestingly, the compounds release curcumin under green light by photoreduction to a Co(II) complex, whereas blue light photolyzes the free curcumin, producing a highly phototoxic product.

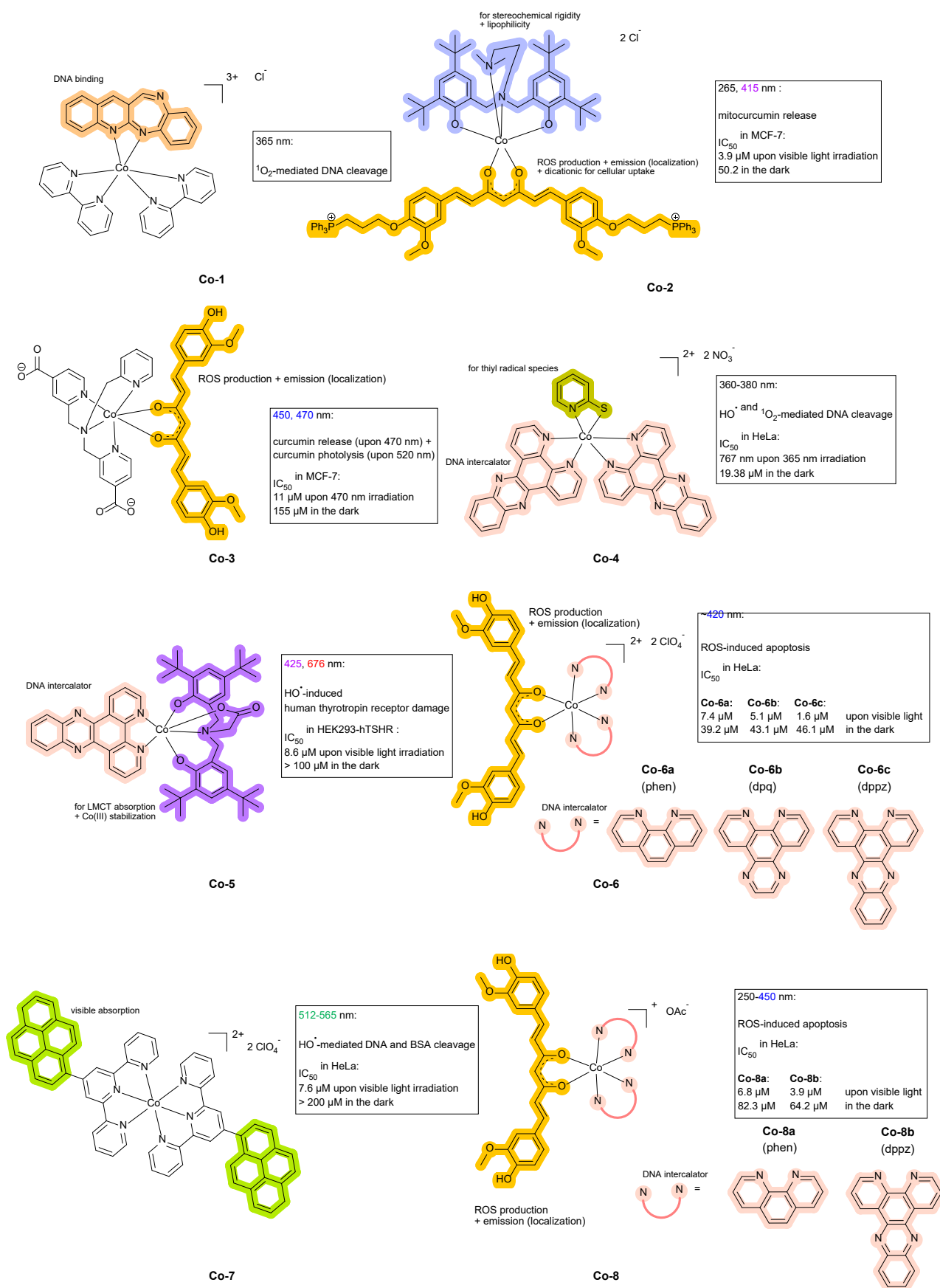


Figure 10: Phototoxic cobalt complexes. In this figure are indicated: the absorption maximum or maxima (coloured if in the visible range), the mechanism responsible for the cell's death, the IC_{50} values upon irradiation and in the dark (and the cell line in which they

have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

Co(III) complexes of pyridine-2-thiol and phenanthroline bases were developed by Chakravarty and co-workers. The dppz derivative (**Co-4**) exhibits good cytotoxicity upon 365 nm irradiation (767 nM in HeLa cells). Complexation of the dppz base to Co(III) centre drastically reduces its dark cytotoxicity in HeLa cells (19.39 μ M when coordinated vs 8.34 μ M for the free base). **Co-4** shows good DNA, BSA and lysozyme cleavage activity upon UV-A light irradiation. In aerobic medium, **Co-4** efficiently cleaves DNA under red light *via* hydroxyl radical and singlet oxygen pathways. Interestingly, the compound is also able to cleave DNA in hypoxic conditions under UV-A irradiation, probably thanks to either sulphide anion radicals or thiyl radical species.¹⁰² Finally, Chakravarty and co-workers published a Co(III) complex (**Co-5**) which is highly phototoxic on Human Embryonic Kidney cells (HEK293) expressing human thyrotropin receptor (HEK293-hTSHR).¹⁰³ HEK293-hTSHR cells are used to evaluate the activity of a compound against thyroid diseases caused by TSH receptor dysfunction. **Co-5** contains a tetradentate phenolate-based ligand appended with lipophilic tetrabutyl groups and a dppz base and shows two absorption bands in the PDT window: a phenolate to-metal band around 425 nm and a d-d band at 676 nm, which allows for photoexcitation with red light. In HeLa cells, **Co-5** is non-toxic – even under irradiation – up to 100 μ M, but moderately phototoxic in normal HEK293 cells (26.5 μ M upon 400-700 nm irradiation vs > 100 μ M in the dark) and shows good phototoxicity in HEK293-hTSHR (8.6 μ M upon visible light irradiation vs > 100 μ M in the dark). Indeed, the human thyrotropin receptor is damaged by hydroxyl radicals under irradiation, which gives hope for treating thyroid pathologies. In 2015, Hussain and co-workers published a series of Co(III) complexes of curcumin displaying promising toxicity upon irradiation in HeLa cells (**Co-6**). As a control experiment, the complexes containing acetylacetonate instead of curcumin indeed did not show any toxicity, even upon irradiation. Complex **Co-6c** with dppz ligands was the more efficient complex of the series with IC₅₀ values of 1.6 μ M upon visible light irradiation in HeLa cells, where it accumulates in the mitochondria, and does not show any toxicity in MCF-10A normal cells.

Co(II) complexes have received much less attention than Co(III) ones so far. Co(II) could be phototoxic thanks to a photoredox pathway instead of acting by a type-II mechanism. Besides, Co(II) should be less prone to reduction by GSH compared to Co(III), which should reduce in-the-dark cytotoxicity. Chakravarty and co-

workers described Co(II) complexes with terpyridine bases capable of cleaving DNA and BSA under UV-A and visible light, *via* formation of singlet oxygen and hydroxyl radical species (**Co-7**).¹⁰⁴ A series of complexes based on Co(II), Ni(II) and Cu(II) with a tetradentate ligand, binding and cleaving DNA in UV-A light via a type-II PDT pathway was published in 2015.¹⁰⁵ The Co(II) complex was the most efficient of the series, with an IC₅₀ of 44.59 μM upon UV-A light exposure and 86.64 μM in the dark on MCF-7 cells.

More recently, two Co(II) complexes of similar structure as **Co-6** also showed good phototoxicity (**Co-8**).¹⁰⁶ **Co-8a** and **Co-8b** exhibit high cytotoxicity in HeLa cells (3.9 and 6.8 μM) and MCF-7 cells (12.2 and 6.1 μM) upon visible light irradiation while remaining significantly less toxic in the dark. Excitingly, **Co-7** complexes were even cytotoxic upon visible light towards multidrug resistant MDA-MB-231 cells (14.1 μM and 9.3 μM) while being far less toxic towards normal lung HPL1D cells (81.0 and 25.6 μM).

2.7 Nickel

Nickel is not an essential element to humans in itself, but is contained in many metalloenzymes,¹⁰⁷ such as urease, often found in human gut bacteria, therefore being indirectly important for humans.¹⁰⁸ Nickel complexes are extensively studied for photoinduced cross-coupling catalysis.¹⁰⁹ Despite these promising photochemical properties, little research has been conducted with nickel, which may be due to the fact that it frequently causes allergies in humans.¹¹⁰ However, a few complexes displaying phototoxicity have been designed. A curcumin-releasing Ni(II) complex of dppz bases was described in 2020 (**Ni-1**, Figure 11), displaying IC₅₀ values of 4.4 μM in HeLa cells under irradiation by visible light, while remaining inactive in the dark.¹¹¹ The curcumin-based band can be excited with visible light, leading to cell death (mainly apoptosis) with a ROS-dependant mechanism. A 2014 article introduces a Ni(II) porphyrazine as well as its Zn(II) analogue.¹¹² However, the Ni(II) complex tends to aggregate, giving poor phototoxicity results in MCF-7 cells. The Ni(II) complex with a tetradentate ligand (**Ni-2**), similarly as the Co(II) complex mentioned above, displayed cytotoxicity on MCF-7 cells (85.14 μM), slightly enhanced upon UV-A light irradiation (47.59 μM).¹⁰⁵ Finally, an attempt to design a Ni(II) complex as a PDT photosensitizer was published in 2020, but no ¹O₂ generation nor phototoxicity were observed.¹¹³

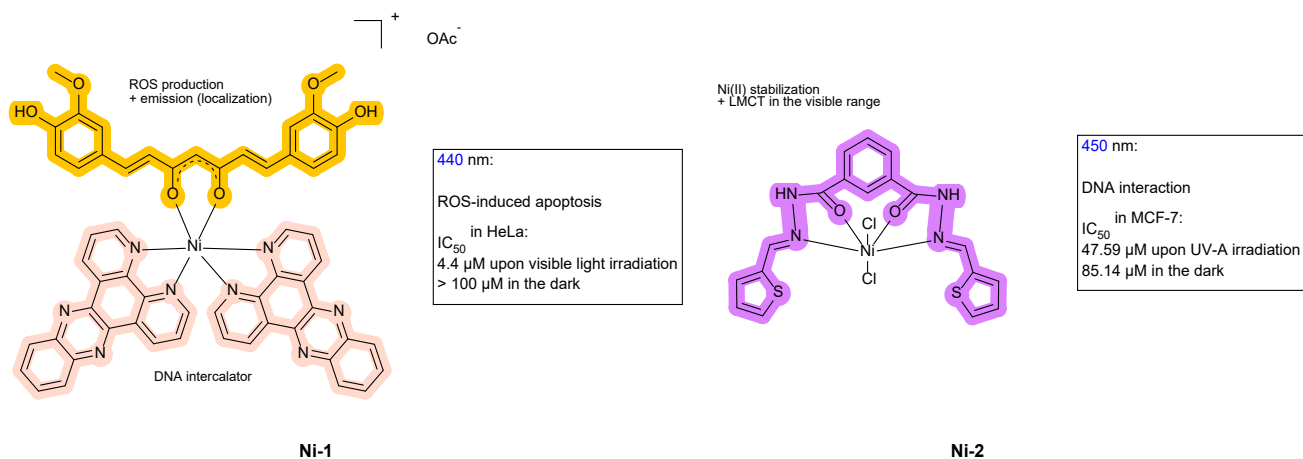


Figure 11: Phototoxic nickel complex. In this figure are indicated: the absorption maximum, the mechanism responsible for the cell's death, the IC₅₀ values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

2.8 Copper

Copper is an abundant and essential metal and is already at the heart of current anticancer research.^{114–116}

Cu(II) complexes (d⁹) share similarities with V(IV) ones (d¹) as they both possess intense low-energy visible bands. However, Cu(II) complexes are easily reduced by thiols to Cu(I) in biological medium, inducing in-the-dark toxicity. Nevertheless, some Cu(II) complexes generating ROS under irradiation were reported. In 2011, Yan and co-workers published a work on two Cu(II) complexes efficiently cleaving DNA upon visible light or UV-A irradiation by generation of ¹O₂ (**Cu-1**, Figure 12).¹¹⁷ **Cu-1b** with its dppz moiety shows especially good binding propensity to calf thymus DNA, which explains its cytotoxicity on HeLa cells (4.40 μM upon visible light exposure and 2.18 μM in upon 365 nm irradiation). However, no cytotoxicity study in the dark were reported for these complexes. In 2013, Chakravarty and co-workers described a Cu(II) complex of curcumin and N-ferrocenylmethyl-L-amino acids (**Cu-2**).¹¹⁸ **Cu-2** displays great cytotoxicity upon visible light irradiation (3 μM vs 48 μM in the dark, HeLa cells) and efficient plasmid DNA cleavage activity was reported. Curcumin is, once again, used as a PS, fluorophore and anticancer agent, while the ferrocene moiety increases the compound lipophilicity and redox activity. The ferrocenyl moiety was also incorporated in complex **Cu-3**, which binds and cleaves DNA upon visible light irradiation by generating hydroxyl radicals.¹¹⁹ As expected, the dppz ligand allows for better DNA binding and cleaving properties; **Cu-3** gives IC₅₀ values of 3.7 μM in

visible light, which is comparable to the oxovanadium(IV) and iron(III) complexes that were previously described.^{54,79} The ferrocenyl moiety is responsible for an enhancement of the cytotoxicity (both in the dark and upon irradiation) compared to its phenyl analogue. Another study on the effect of ferrocenyl moiety on phototoxic Cu(II) complexes appended with L-tryptophan was published in 2011 (**Cu-4**).¹²⁰

The same team published other Cu(II) complexes of curcumin appended with non-iodinated and iodinated BODIPY moiety (**Cu-5a** and **Cu-5b** respectively).¹²¹ **Cu-5a** with its non-iodinated BODIPY ligand is emissive, which allowed the authors to determine the mitochondrial localization of the complex in HeLa cells. **Cu-5b** complexes generate ROS upon visible light irradiation, leading to HeLa cells apoptosis. **Cu-5b** containing the diiodo BODIPY moiety displays better cytotoxicity values upon visible light irradiation (2.8 μM in HeLa cells vs 7.9 μM for **Cu-5a**) because of a better ISC. In addition, they published other BODIPY-Cu(II) conjugates lacking the curcumin ligand (**Cu-6**).¹²² Cellular imaging with **Cu-6a** showed – again – mitochondrial localization in HeLa and MCF-7 cells. **Cu-6b** with the diiodinated BODIPY displayed a significant enhancement of cytotoxicity upon visible light irradiation: 0.04 μM (vs 24.65 μM in the dark).

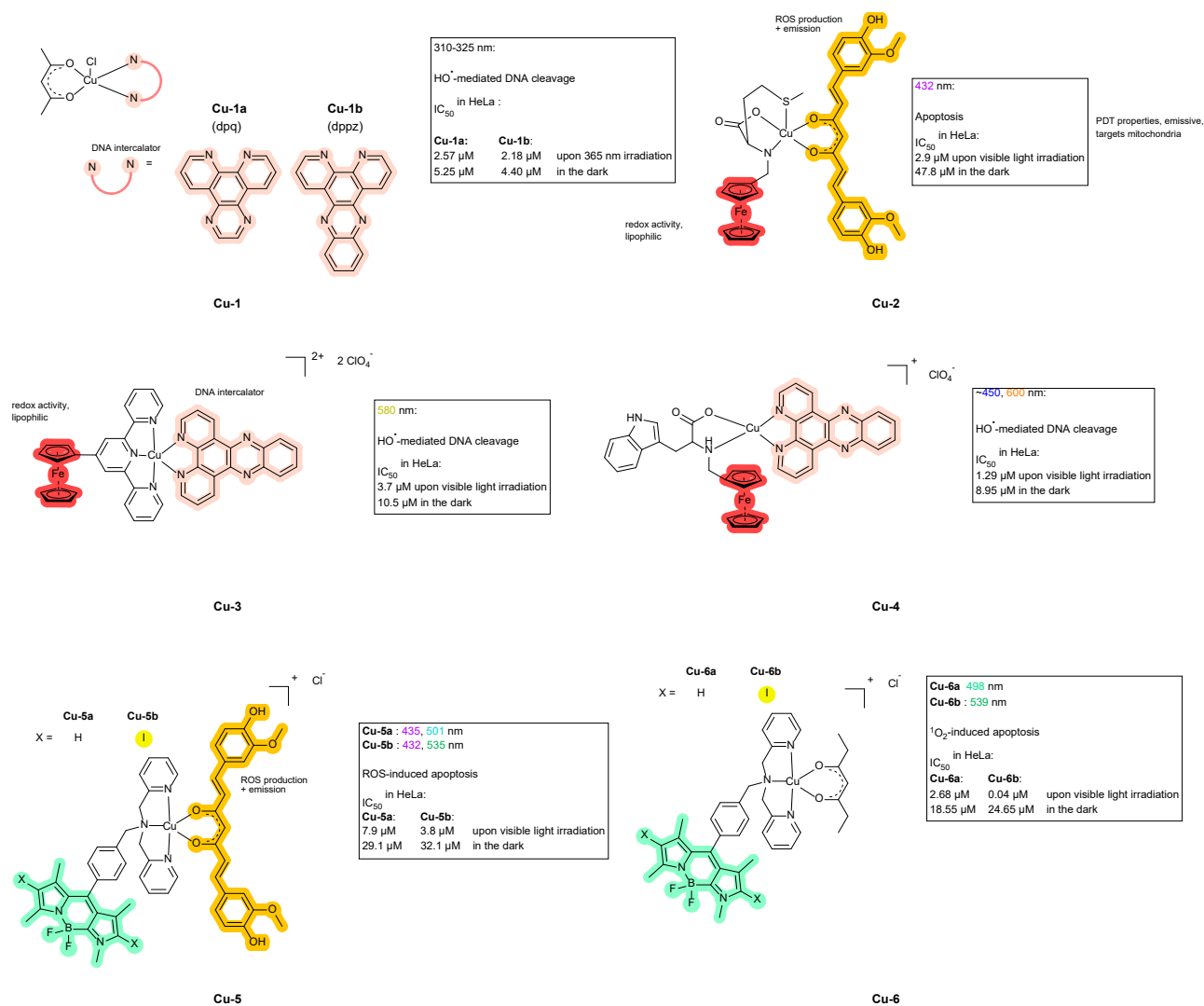


Figure 12: Phototoxic copper complexes. In this figure are indicated: the absorption maximum, the mechanism responsible for the cell's death, the IC₅₀ values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

More recently, Chakravarty and co-workers also published Cu(II) complexes of curcumin and acridine-dppz ligands (**Cu-7**, Figure 13) – as well as its Zn homologue (**Zn-2**, see below Figure 14).¹²³ **Cu-7** displayed very good photodynamic activity in HeLa, MCF-7 and HepG2 cells: apoptosis is provoked by both type I and II mechanisms. Moreover, the fluorescent acridinyl moiety allowed for cellular localization, which showed that **Cu-7** accumulates in the cytosol. However, as for many Cu(II) complexes, **Cu-7** displays in-the-dark cytotoxicity, contrarily to its Zn analogue (see below). Phototoxic Cu(II) complexes with Schiff base ligands were also designed for PDT (**Cu-8**).¹²⁴ **Cu-8** was quite cytotoxic upon visible light irradiation in human squamous carcinoma cells (SCC15) and in basal carcinoma cells (BCC) and less toxic in the dark. The charge

transfer from the phenolate π orbitals to the metal $d\pi^*$ orbitals is responsible for a visible LMCT absorption band. DNA cleavage occurs upon blue light irradiation and not in the dark. Moreover, the cells treated with **Cu-8** exhibit nuclei morphological changes and cell apoptosis. However, despite the use of a tridentate Schiff base as a stabilizer, the Cu(II) complex still exhibits significant cytotoxicity in the dark (7.25 μ M in HeLa cells).

Metalloporphyrins are expected to give interesting photo-induced toxicity results, thanks to the Q-band – in the near-IR region – characteristic for that kind of extended π -conjugated systems. Copper porphyrin were therefore investigated as PSs. In 2015, a paramagnetic Cu(II) porphyrin displayed enhanced cytotoxicity upon red light (> 600 nm) irradiation (**Cu-9**).¹²⁵ Tetraaryl porphyrins appended with L-glutamate (for better hydrophilicity and phototoxic activity) and their Cu(II) and Zn(II) complexes were studied in 2016.¹²⁶ However, complexation to copper decreased the phototoxic activity of the porphyrins. This could be due to

the paramagnetic nature of the Cu(II) complex, generally prone to non-emissive deactivation from the singlet excited state.

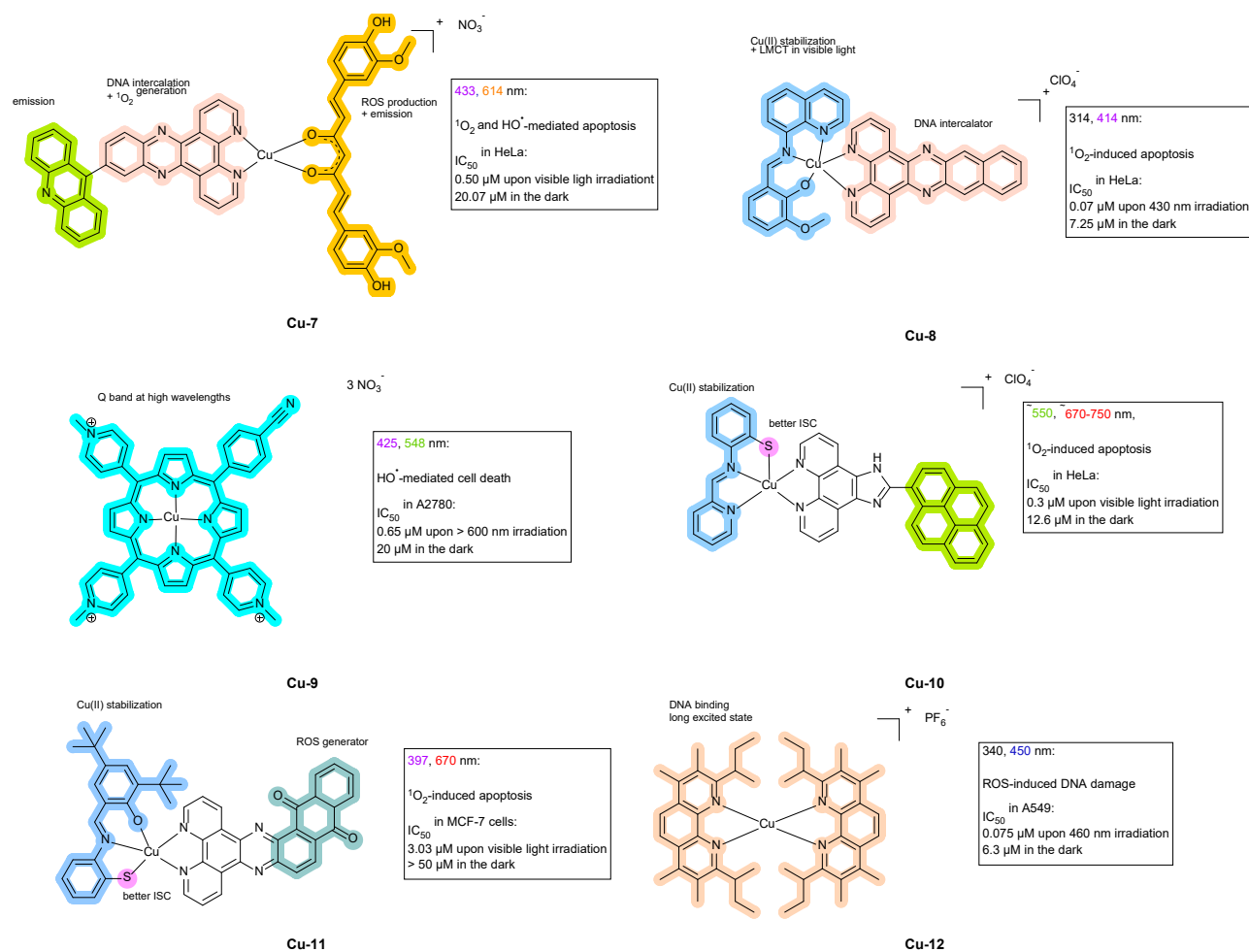


Figure 13: Phototoxic copper complexes. In this figure are indicated: the absorption maximum, the mechanism responsible for the cell's death, the IC_{50} values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

Roy and co-workers studied the role of S-coordination in Cu(II) complexes for PDT applications (**Cu-10**).¹²⁷

They studied complexes coordinated to O or S, which were all toxic in the dark ($\sim 10 \mu\text{M}$, HeLa cells) but the cytotoxicity was significantly enhanced upon irradiation for all complexes ($\sim 1 \mu\text{M}$). S-coordinated complexes possess low-lying and long-lived excited states, which favours ISC and hence singlet oxygen generation. Indeed, upon visible light irradiation, S-coordinated complexes are more cytotoxic than O-coordinated ones.

The d-d band appears in the range of 670-750 nm and the pyrenyl moiety engages in an LMCT band around 550 nm. **Cu-10** is particularly phototoxic ($0.3 \mu\text{M}$ upon visible light irradiation) and induces apoptosis thanks

to the photosensitization of the *S*-coordination and the pyrenyl moiety. Two years later, the same team designed complexes with remarkable cytotoxicity upon visible irradiation (2-11 μM), thanks – once again – to the increased photosensitization with *S*-coordination and to the addition of an anthraquinone moiety (**Cu-11**).¹²⁸ The in-the-dark cytotoxicity is significantly reduced ($> 50 \mu\text{M}$ in HeLa cells) contrarily to most other Cu(II) complexes. **Cu-11** possess a reduction potential ($E_{1/2} = -0.46 \text{ V}$) far beyond the biological redox window, therefore inhibiting the reduction of the Cu(II) complex, which might explain this relatively low dark cytotoxicity. A Cu(II) complex, analogue of **Ni-2** (Figure 11), displays slightly enhanced phototoxicity upon UV-A irradiation on MCF-7 cells (53.60 μM vs 131.70 in the dark).¹⁰⁵ Another Cu(II) complex was designed as a PS, but had a very poor ability to generate singlet oxygen: exposing the cells to light did not really change their viability.¹¹³ To avoid Cu(II) reduction by thiols in cells, the use of Cu(I) complexes could be another solution, that has only been scarcely explored, however, because of the instability of the majority of four-coordinated Cu(I) complexes. In 2018, Khnayzer and co-workers published their work on a cuprous bis-phenanthroline complex for PDT (**Cu-12**).¹²⁹ **Cu-12** shows an MLCT band around 460 nm and an IL band in the UVA range. Even though rather cytotoxic in the dark, the complex was still quite phototoxic upon blue irradiation on A375 (human malignant melanoma) and A549 (human lung carcinoma) cell lines, thanks to its extended excited state lifetime. DNA damage was observed in the dark, yet significantly enhanced upon irradiation thanks to the generation of ROS.

2.9 Zinc

Zinc is a key element in many enzymes for their activities or their structure (such as in Zn finger proteins) and is therefore essential to humans. Zinc exists in two oxidation forms: Zn(0) and Zn(II), and is mostly redox-inactive in biological conditions. Zn(II) complexes possess a closed-shell d^{10} configuration, resulting a low-energy excited states and allowing for LC absorption bands. Moreover, adding substituents to the ligands enhances the yield of the triplet state for these diamagnetic complexes.¹³⁰ A bis(terpyridine)zinc(II) complex possessing two-photon absorption properties and acting as type I and type II PDT agent was recently reported.¹³¹ Unlike the free ligand, the Zn complex has a much smaller singlet-triplet gap: this allows for

better ISC (which is confirmed by a lower fluorescence), and thus better singlet oxygen generation. This complex is also capable of reducing dioxygen into superoxide radicals and the two-photon absorption capacity allows for near-IR absorption. Moreover, the cationic and lipophilic ligand allow excellent mitochondria targeting.

A Zn(II) analogue of the previously reported Cu(II) complex of curcumin and dppz appended with an acridinyl moiety (**Cu-3**, Figure 12) showed very good photodynamic activity in HeLa, MCF-7 and HepG2 cells (**Zn-1**, Figure 14).¹²³ This green-emissive complex revealed cytosolic localization. **Zn-1** is stable in physiological medium (10% FBS-DMEM), contrarily to the free curcumin. Apoptosis is caused by both singlet oxygen and hydroxyl radical pathways. The Zn(II) analogue of **Cu-4** was studied (**Zn-2**).¹²⁰ Zn(II) is redox inactive, and is not involved with the ferrocenyl, contrary to the Cu(II) complex **Cu-4**. **Zn-2** is therefore a mediocre DNA cleaver and is non-toxic on HeLa cells up to 80 μM both upon irradiation and in the dark. In the 2014 article describing Ni(II) and Zn(II) complexes (see **Ni-2**), the zinc derivative displayed promising results, contrary to the nickel one which tended to aggregate.¹¹² No IC_{50} measures were performed, however, viability tests on MCF-7 cells have concluded that this Zn complex is not toxic in the dark up to 30 μM while being significantly toxic upon 631.4 nm irradiation.

In addition, Zn(II) is particularly well suited for incorporation in macrocycles such as porphyrins – for application in PDT – because of its long triplet state lifetime, which can favour $^1\text{O}_2$ production.¹³² In the absence of a complexed metal ion, these macrocycles absorb in the visible range with a Soret band around 440 nm and a Q band around 560 nm. An article describing metalloporphyrins, including a Zn(II) one, as phototoxic compounds was published in 2015.¹²⁵ Unlike the Cu(II) porphyrin (**Cu-5**), the Zn(II) one (**Zn-3**) does not intercalate DNA, because of its geometry which imposes an axial configuration of one of the ligands. The compound showed moderate phototoxicity under red light in HeLa cells (0.5 μM upon >600 nm irradiation vs 11.5 μM in the dark) and slightly better activities against a cisplatin-resistant cell line (A2780cis), which gives hope for new PDT agents active against persistent tumours. In 2017, a Zn(II) porphyrin with *N*-methylpyridinium groups – for water solubility – was shown to exhibit good phototoxicity on A549 cells, with an IC_{50} of 75 nM under irradiation, compared to more than 100 μM in the dark.¹³³ More recently, another

Zn(II) porphyrin was reported, with IC₅₀ values of 2.01 μM upon irradiation while remaining non-toxic in the dark.¹³⁴ In 2019, bis(dipyrrinato)Zn(II) complexes were designed as potential PDT PSs (**Zn-4** being one of them).¹³⁵ The two dipyrrinato ligands are structurally similar to “half-porphyrins”; they display comparable excited states, while avoiding classic porphyrin drawbacks such as aggregation and a tedious synthesis. As mentioned for the BODIPY moiety in **V-8**, better ISC can be obtained from the presence of iodine atoms because of an increased spin-orbit coupling. The dipyrrinato ligands were therefore iodinated; however, the excited states of the complexes are significantly quenched in polar solvents. To overcome this issue, **Zn-4** was encapsulated in a polymer (of PEGylated phospholipids) and tested on cells as well. The complexes showed good phototoxicity in different cell lines as well as in 3D multicellular tumour spheroids (MCTS) without dark cytotoxicity. The encapsulation strategy was particularly successful, with an IC₅₀ of 1.2 μM in HeLa cells upon 500 nm irradiation (vs > 100 μM in the dark). A few other articles described phototoxic Zn(II) porphyrins as promising type II PDT agents: a metronidazole-appended Zn porphyrin,¹³⁶ a porphyrin with triethylene glycol moieties – for solubility – and ethynylene – for absorption –,¹³⁷ a picolyl Zn porphyrin nanostructure,¹³⁸ and an anionic porphyrin with carboxylate moieties.¹³⁹

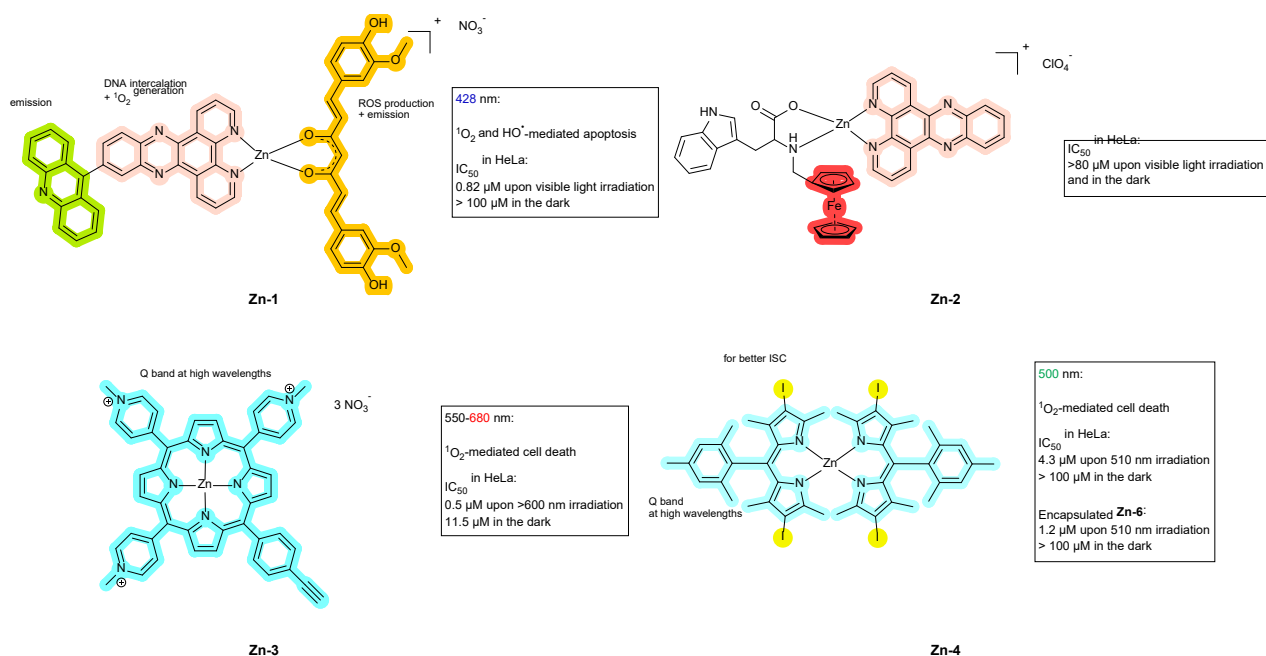


Figure 14: Phototoxic zinc complexes. In this figure are indicated: the absorption maximum, the mechanism responsible for the cell's death, the IC₅₀ values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

However, as most porphyrins strongly absorb in the range of 400-600 nm, it can induce skin phototoxicity when the patient is in contact with the sun/light; thus patients may have to take precautions and avoid light exposure after PDT treatment.¹⁴⁰ Unlike porphyrins, phthalocyanines (Pcs) exhibit weak absorption in this range, which overcomes this skin sensitivity issue. Pcs are synthetic dyes that were first synthesized in the early 20th century;¹⁴¹ they are porphyrins with isoindole units replacing the pyrroles and display a weak Soret band in the UV/blue zone and a Q-band (just like for porphyrins) around 680 nm. The coordination to a diamagnetic element in the central cavity also allows for high triplet quantum yields, making them good singlet oxygen generators. This explains the extensive research in Zn phthalocyanines (ZnPcs) that have been undertaken in recent years. On this topic, two reviews have extensively covered ongoing research on phthalocyanines as PSs, including phototoxic ZnPcs.^{142,143} The review by Dumoulin and co-workers presents – by examples – strategies to optimize the photochemical or biological qualities of phthalocyanines as well as ways to excite or activate them,¹⁴² while the review by Marino and co-workers particularly focuses on the biological effects of ZnPcs, including cell death mechanisms for example.¹⁴³ Although phthalocyanines have exceptional theoretical qualities for PDT, they suffer from aggregation problems in solution, which often makes their application *in vivo* tricky. To prevent this, several techniques were developed, such as, for example, the incorporation of a charged moiety: either positive^{144–148} or negative.^{149,150} ZnPcs can also be encapsulated in cyclodextrins,¹⁵¹ liposomes,^{152–154} micelles,^{155–158} or nanoparticles (that can consist of polymers,^{159–161} silica,^{162,163} gold,^{164,165} or TiO₂¹⁶⁶). Two ZnPcs are already in phase II clinical trials: CGP55847, which is a liposomal formulation of ZnPc, used against squamous cell carcinomas,¹⁶⁷ and Photocyanine, a di-(potassium sulfonate)-di-phthalimidomethyl ZnPc which was in clinical trial in China against human hepatocellular carcinoma up to phase II (Figure 15).^{168,169}

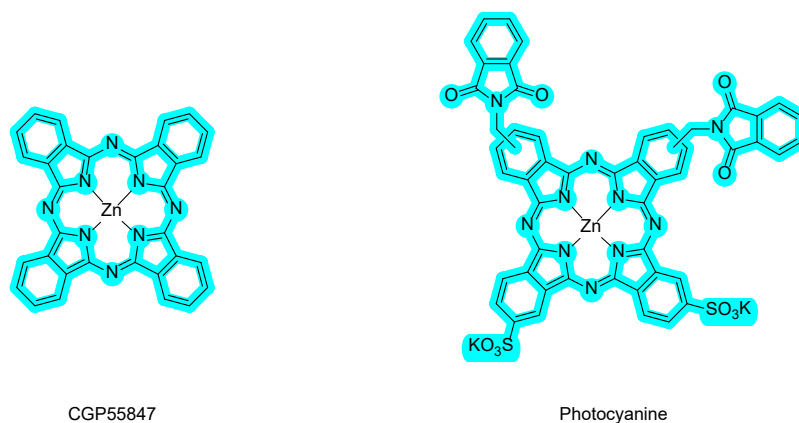


Figure 15: Zinc phthalocyanines that are currently in clinical trial.

As this topic is already extensively covered by Dumoulin and Marino, we will only describe the most recent and more representative examples herein. A ZnPc published in 2013 was synthesized with 16 imidazolyl moieties positively charged for improving the solubility and diminishing the risk of aggregation (**Zn-5**, Figure 16).¹⁷⁰ **Zn-5** is highly phototoxic on HeLa cells with IC_{50} values of 36.7 nM upon red light irradiation, but is not cytotoxic in the dark ($IC_{50} = 628 \mu\text{M}$). A glycerol-appended ZnPc was published in 2014 (**Zn-6**).¹⁷¹ The glycerol substituents were added to improve the ZnPc solubility and since they are electron-donating alkoxy moieties, they could also induce a shift of absorption towards the red. The resulting compound displays good phototoxicity on HCT-116 (3.2 μM), HSC-2 (2.8 μM) and MCF-7 cells (2.9 μM) while remaining non-toxic in the dark (> 100 μM for all cell lines). In 2018, a tumour-pH responsive ZnPc containing amino moieties was published (**Zn-7**).¹⁷² The non-protonated amino moieties quench the photoactivity of **Zn-7** via photoinduced electron transfer. When protonated, the photoactivity of **Zn-7** is restored. Therefore, in slightly acidic conditions such as the ones found in tumours, the complex can reach a triplet state, allowing for singlet oxygen generation and fluorescence. **Zn-7** indeed displays very high anti-tumour activity at a slightly acidic pH (6.4), while remaining non-toxic when pH is around 7.4. Moreover, **Zn-7** is fluorescent and can be localized in cells. **Zn-7** displays IC_{50} values of 0.20 μM on 4T1 cells under light irradiation (2.5 J $\cdot\text{cm}^{-2}$). *In vivo* studies were conducted on mice, showing a strong tumour-growth inhibition activity of **Zn-7** upon irradiation. An article recently described ZnPcs bearing several amphiphilic pyridinium groups and bulky axial ligands to

minimize aggregation (**Zn-8**).¹⁷³ The Q-band of **Zn-8** was observed around 675 nm. Upon exposure to low irradiation (1.5 J/cm²), **Zn-8** was highly toxic (IC₅₀ = 5.3 μM vs > 100 μM in the dark).

ZnPc research for PDT is very active: in 2021 alone, several articles have been published that use the strategies mentioned above. To improve the solubility of ZnPcs, encapsulation in liposomes,¹⁷⁴ micelles,^{175,176} vesicles¹⁷⁷ or nanoparticles were conducted.^{178,179} Some nanoparticles were even used in combination with chemotherapeutic strategies, with the anticancer drugs soranefib¹⁸⁰ and doxorubicin.¹⁸¹ This dual photo- and chemotherapeutic strategy has also been implemented with molecular complexes, with a histone deacetylase inhibitor¹⁸² or with immunotherapeutic activity.¹⁸³ We can also cite a recent work on ZnPcs that target tumours through PEG functionalization.¹⁸⁴ An article presented a ZnPc appended with four 2-pyridones that displays three advantages for PDT (**Zn-9**).¹⁸⁵ First, **Zn-9** can be excited by both 665 and 808 nm, allowing for both superficial and deep tumour treatment. Second, **Zn-9** is able to slowly release ¹O₂: the 2-pyridones can be oxidized into peroxides by ¹O₂ and the “stored” ¹O₂ can then be slowly released at 37 °C. Third, **Zn-9** can down-regulate the hypoxia-inducible factor 1 (HIF-1) expression (a transcription factor that responds to hypoxia). This would enhance the levels of O₂ for a better PDT effect. **Zn-9** was not water-soluble in itself but was solubilized with Cremophor EL, a non-ionic surfactant. The resulting compound was highly phototoxic on HeLa cells: the cell survival dropped when irradiated with 665 or 808 nm light.

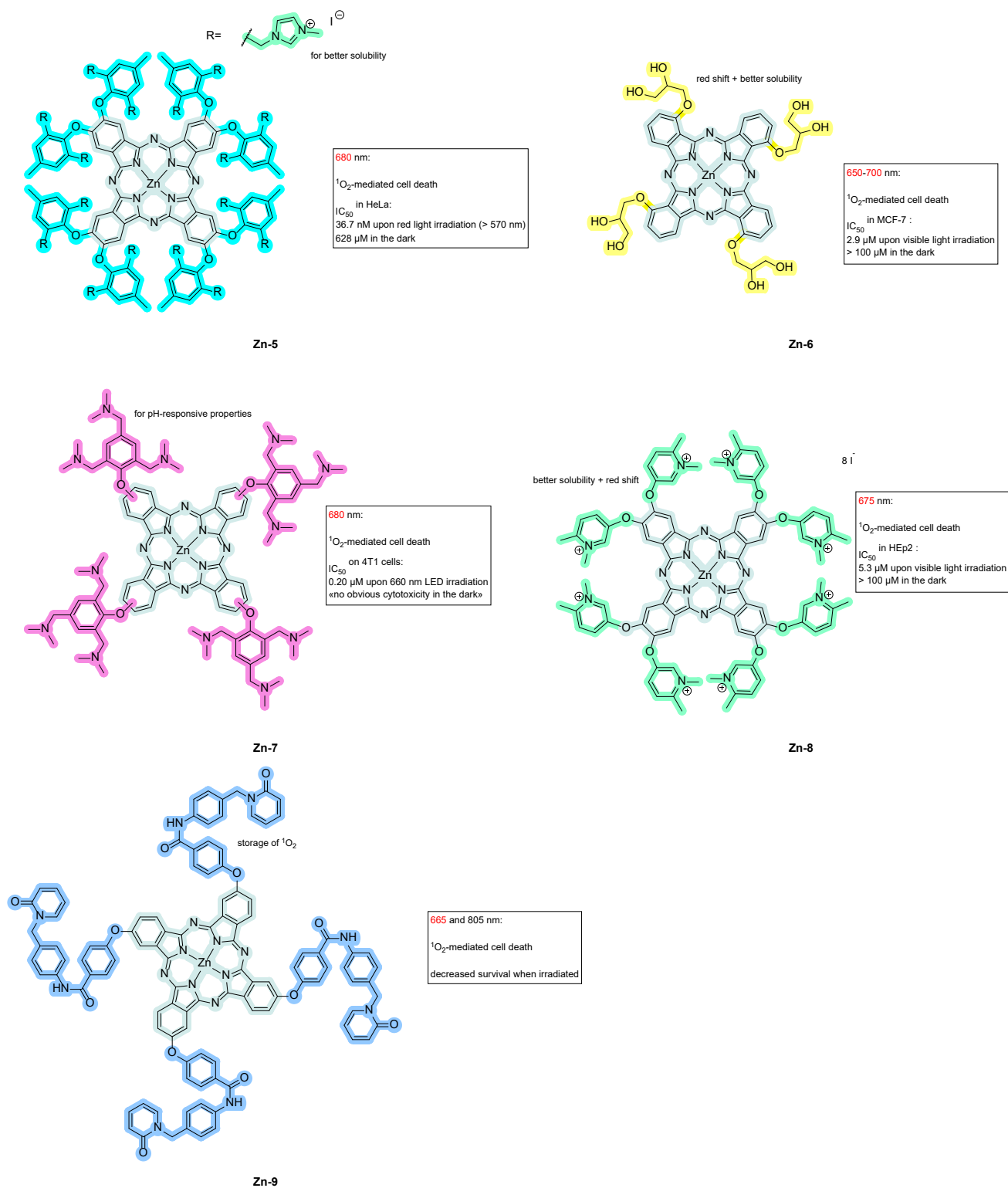
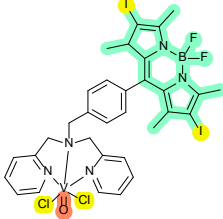
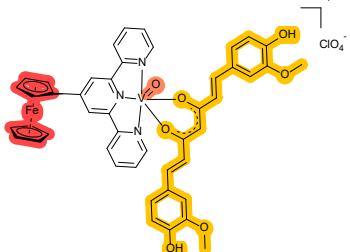
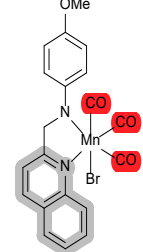
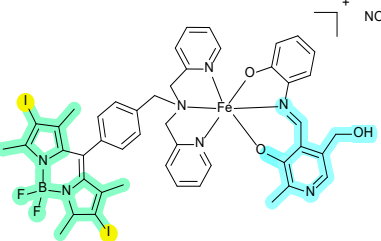
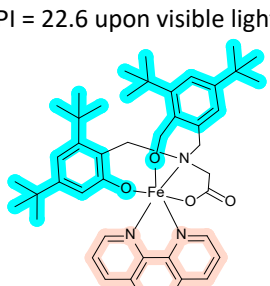
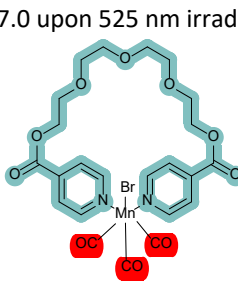
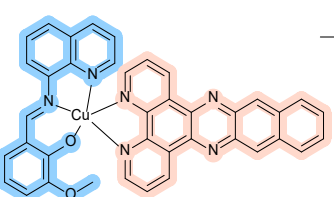
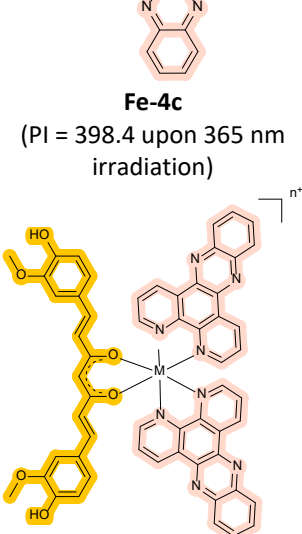
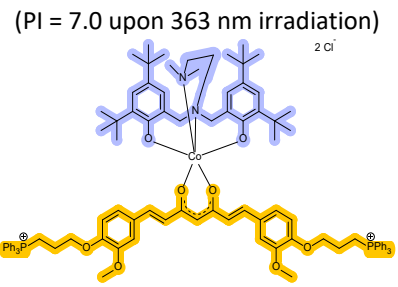
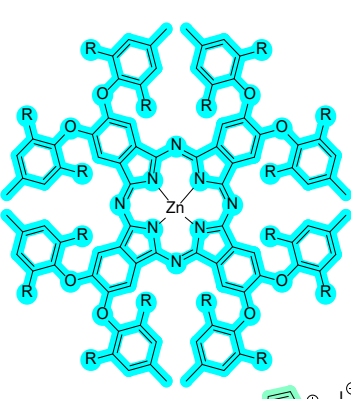
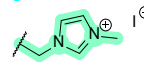
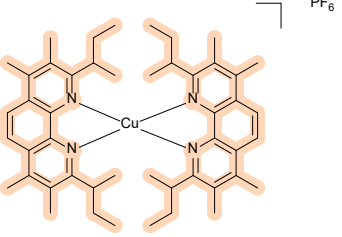
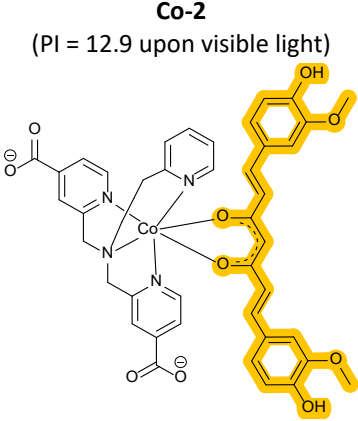


Figure 16: Phototoxic zinc phthalocyanine complexes. In this figure are indicated: the absorption maximum, the mechanism responsible for the cell's death, the IC₅₀ values upon irradiation and in the dark (and the cell line in which they have been measured). The ligands are highlighted and annotated when they display certain properties of interest. Visible light is defined as a range between 400 and 700 nm.

3 Conclusion

With cancer being one of the main causes of death in the world, the development of anticancer drugs is an essential research topic. To avoid undesirable side effects, the use of a benign stimulus, such as light, to activate the molecule at a given location and time is an effective and elegant method. In the context of anticancer photodynamic therapy, metal-base PS have proven extremely versatile and promising. However, complexes based on heavy metals (Pt, Ru, Os, Ir), which are mostly used today, would often result in significant dark cytotoxicity and considerable ecological impact as well as high drug prices. There is therefore an urgent need to turn to lighter and less rare metals such as first row transition metals. Despite their advantages on these latter aspects, they display challenging chemical properties, because of the short-lived metal-centred excited states, narrow vibrational levels, and sometimes unstable oxidation states. This review has highlighted the successful exploratory work of several groups in order to overcome these issues. In Table 1 are summarized some of the most promising complexes presented in this review, classified according to their mode of action. The phototherapeutic index, which is a key indicator of the phototoxicity of the compound (IC_{50} upon irradiation divided by IC_{50} in the dark), is indicated in brackets in the table.

Table 1: Some complexes based on first-row metals that display a phototoxic activity, classified by type of reaction. The phototherapeutic index PI (the ratio between the IC₅₀ in the dark and under irradiation) is indicated between brackets.

Type II PDT (¹ O ₂ generation)	Type I PDT (other ROS generation)	PACT (ligand release or exchange)
 <p>V-8 (PI = 667 upon visible light)</p>	 <p>V-4 (PI = 22.6 upon visible light)</p>	 <p>Mn-3 (PI = 7.0 upon 525 nm irradiation)</p>
 <p>Fe-10 (PI = 909.1 upon visible light)</p>	 <p>Fe-4c (PI = 398.4 upon 365 nm irradiation)</p>	 <p>Mn-4 (PI = 7.0 upon 363 nm irradiation)</p>
 <p>Cu-8 (PI = 103.6 upon 430 m irradiation)</p>	 <p>Co-6c (M = Co n = 2; 2ClO₄⁻) (PI = 28.8 upon visible light)</p> <p>Ni-1 (M = Ni n = 1; AcO⁻) (PI = 22.7 upon visible light)</p>	 <p>Co-2 (PI = 12.9 upon visible light)</p>
 <p>Zn-5 (PI = 17112 upon >570 nm irradiation)</p> <p>R = </p>	 <p>Cu-12 (PI = 84 upon 460 nm irradiation)</p>	 <p>Co-3 (PI = 14.1 upon 470 nm irradiation)</p>

The proposed solutions in this review are varied and depend greatly on the metal. For some metals, polydentate ligands are used to stabilize the metal oxidation state. Redox properties can be enhanced by moieties such as ferrocene for example. For metals possessing low-lying MC states, the use σ -donor ligands has proven to be an effective method to promote visible absorption, thanks to ligands-to-metal charge transfers which can be rationalized by DFT studies. In many of the studies presented in this review, DNA cleavage can be achieved with ROS-generating complexes containing DNA intercalating ligands. Other ligands allow targeting of sensitive organelles such as mitochondria or the endoplasmic reticulum. Some other strategies are based on the release of a cytotoxic molecule such as curcumin or carbon monoxide upon irradiation. Overall, we hope this review will provide an asset to help in the rational design of phototoxic complexes based of first-row transition metals. This research field should allow for the development of affordable and sustainable anti-cancer drugs with reduced side effects.

AUTHOR INFORMATION

Corresponding Authors

* e-mail: kevin.cariou@chimieparistech.psl.eu; gilles.gasser@chimieparistech.psl.eu

ORCID:

Lisa Gourdon: 0000-0003-0932-7838

Kevin Cariou: 0000-0002-5854-9632

Gilles Gasser: 0000-0002-4244-5097

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About the graphical abstract

The graphical abstract was created by L. G., with the kind assistance of Erkan Narmanli, drawing inspiration from a 1930's poster from the French Ministry of Public Health, which can be seen at the Musée Curie, 1 rue Pierre et Marie Curie - 75005 Paris. The crab represents the cancer (which derives from the Greek *καρκίνος*) and the sword the therapeutic strategy to eradicate it.

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