doi:10.2533/chimia.2025.838 Chimia 79 (2025) 838–847

Guided by Enzymes: Targeted Photodynamic Therapy as a Strategy for Precision Medicine

Lara Sereina Wild,[a] Joel Whitcher,[a] Thibaud Rossel,[b]* Kevin Cariou,[a]* and Gilles Gasser[a]*

Abstract: Photodynamic therapy (PDT) is a clinically proven, non-invasive cancer treatment that enables precise spatial and temporal control of cytotoxicity. Yet, many current photosensitisers (PSs) suffer from poor tumour specificity, limiting their effectiveness. Targeted photodynamic therapy (tPDT) addresses this by directing PSs to selectively accumulate in tumour tissue. Among the emerging strategies, enzyme targeting stands out as a powerful approach. This review explores enzyme-targeted PDT using metal-based PSs conjugated to small-molecule enzyme inhibitors — a dual-action design that enables tumour destruction while blocking key pro-tumour signalling pathways. Five distinct proteins with enzymatic activity such as carbonic anhydrase (CA), cathepsin B, cyclooxygenase (COX), epidermal growth factor receptor (EGFR), and heat shock protein 90 (Hsp90) are presented through selected conjugates. These cases underscore the versatility of tPDT in achieving precise tumour targeting. By enhancing therapeutic efficacy, minimising off-target toxicity and collateral damage, and ultimately improving patient safety, enzyme-directed tPDT bridges targeted therapy, photomedicine, and precision oncology — setting the stage for next-generation cancer treatments.

Keywords: Enzyme inhibitors · Medicinal Inorganic Chemistry · Photodynamic therapy (PDT) · Photosensitisers · Precision medicine

1. Introduction

Cancer is a leading cause of mortality worldwide, and conventional treatment approaches such as radiotherapy, chemotherapy, and surgical resection are widely employed. However, for cancers with poor prognosis or high recurrence rates, the development of innovative therapeutic strategies remains imperative.[1] Photodynamic therapy (PDT) is a non-invasive therapeutic modality for tumour treatment that gained prominence in oncology following the landmark publication by Dougherty and colleagues in 1978.[2,3] PDT employs a photosensitiser (PS), which is non-toxic in the absence of light but becomes cytotoxic upon light irradiation. The PS is excited to a higher electronic state through photon absorption, which gives rise to two distinct photochemical reaction pathways (Fig. 1).[4] In a Type I photochemical process, the PS undergoes electron abstraction from a proximal electron-donating substrate and transfers its extra electron to molecular oxygen (O_2), generating reactive oxygen species (ROS). In a Type II photochemical reaction, the triplet excited state of the PS undergoes non-radiative energy transfer to molecular oxygen ($^3O_2$), thereby generating excited singlet oxygen ($^1O_2$).[5] Both ROS and $^1O_2$ are highly cytotoxic and induce cell death.

PDT has garnered significant attention as an alternative treatment due to its spatiotemporal precision, enabling selective tumour eradication while minimising side effects.[6] Both metal-free and metal-based PSs are currently undergoing clinical evaluation or have already received local therapeutic approval.[7] However, current PDT agents present several inherent limitations.[8–10] Their strict dependence on molecular oxygen to exert cytotoxic effects markedly reduces efficacy in hypoxic tumour microenvironments, a characteristic feature of most solid tumours. In addition, their excitation wavelengths frequently lie in the UV or visible range, which restricts tissue penetration. Furthermore, most PDT agents lack tumour selectivity, which can result in unwanted photodamage to healthy tissue, either adjacent to the tumour or exposed to sunlight.[11] To overcome these limitations, various strategies are being explored and, ideally, combined, including the use of PSs with absorption in the near-infrared region or with oxygen-independent photoreactivity.[12] Nevertheless, tumour selectivity remains a major limitation, which has spurred the development of diverse targeting strategies.

To address the issue of selectivity, PSs can be designed in such a way that they preferentially accumulate within tumour tissue. Tumour targeting can be achieved through passive, active, and stimuli-responsive strategies. Passive targeting relies on the enhanced permeability and retention (EPR) effect, where nanocarriers such as liposomes or exosomes accumulate in tumour tissue as a result of leaky vasculature combined with impaired lymphatic clearance.[13] Stimuli-responsive systems exploit the unique features of the tumour microenvironment, such as acidic pH, redox gradients, or elevated enzyme activity, to achieve site-specific activation of photosensitisers.[14–18] In addition, active targeting employs specific ligands, including antibodies, peptides, aptamers, or small-molecule inhibitors, to direct PSs towards tumour-associated proteins or enzymes.[19–31]

While all three strategies have been extensively explored in recent years, this review specifically focuses on enzyme-inhibitor-based tPDT employing metal-based PSs since such types of PSs were shown to hold great promises.[32,33] Such PSs are characterised by their conjugation to enzyme inhibitors to actively target the cells expressing the particular enzymes (Fig. 2). This approach provides dual benefits: selective delivery to tumours *via* tumour-associated enzymes and concomitant modulation of tumour-promoting pathways. It is important to mention at this point that conjugating a PS to the inhibitor introduces the risk of altering its inhibitory function due to the steric and electronic influence of the bulky metal complex. Consequently, the choice of

*Correspondence: Dr. T. Rossel, E-mail: thibaud.rossel@unine.ch; Dr. K. Cariou, E-mail: kevin.cariou@chimieparistech.psl.eu; Prof. G. Gasser, E-mail: gilles.gasser@chimieparistech.psl.eu.
[a]Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Laboratory for Inorganic Chemical Biology, Paris 75005, France;
[b]Institute of Chemistry, University of Neuchâtel, Avenue de Bellevaux 51, Neuchâtel, Switzerland.

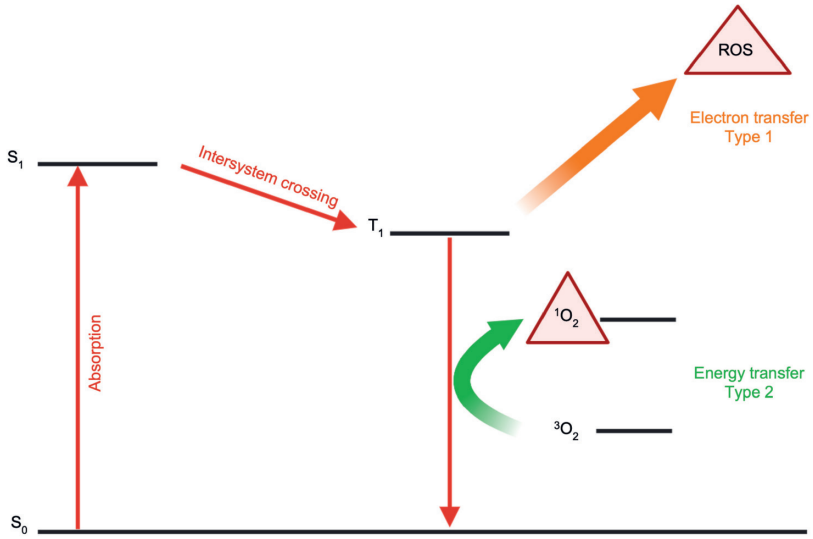


Fig. 1. Energy diagram of Photodynamic Therapy pathway.

the ligand used for conjugation is a critical factor in determining the overall performance of the resulting compound. Herein, the targeting of Carbonic Anhydrase (CA), Epidermal growth factor receptor (EGFR), Cathepsin B, Cyclooxygenase (COX) and Heat shock protein 90 (Hsp90) will be discussed. For each target, representative metal-based photosensitiser–inhibitor conjugates are examined regarding their design, photophysical properties, and therapeutic efficacy, highlighting both the therapeutic potential and challenges of enzyme-targeted PDT.

2. Carbonic Anhydrase (CA)

Carbonic anhydrases (CAs) are a family of Zn(II)-containing metalloenzymes that catalyse the reversible hydration of carbon dioxide ($CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$).[34,35] Carbonic anhydrase IX (CAIX) is a transmembrane protein that regulates the pH within the tumour microenvironment (TME). In hypoxic tumours, elevated glycolytic activity results in excessive lactate production, thereby acidifying the extracellular milieu. CAIX contributes to pH buffering, maintaining intracellular homeostasis and thus supporting tumour cell survival.[34] Consequently, CAIX is predominantly overexpressed in tumours owing to their hypoxia and minimally expressed in most healthy tissues, making it an ideal target for tumour-specific delivery strategies providing dual benefits: selective delivery to hypoxic tumour regions and concomitant inhibition of CAIX activity, thereby impairing tumour cell survival.[36] Several CA inhibitors have been identified and extensively characterised by De Simone and coworkers, who elucidated their distinct binding modes.[37] Among the many different CA inhibitors, sulfonamide groups (presented as purple dots in Fig. 3) are the most commonly used in clinical applications. The inhibitory function of the sulfonamide group is based on the coordination of its deprotonated nitrogen atom to the catalytic Zn^{2+} ion. This interaction involves both electrostatic attraction between the negatively charged inhibitor and the zinc cation, and the formation of hydrogen bonds between the remaining hydrogen on the nitrogen and neighbouring amino acid residues within the active site.[38] Building on this biological rationale, several benzenesulfonamide based CAIX-targeted PSs have been reported and will be discussed in the following section (Fig. 3).

Since certain tumours, such as triple-negative breast cancer and colorectal carcinoma, are immunologically inert ('cold'), immune checkpoint blockade (ICB) therapies often show limited efficacy in these cancer types. To overcome this limitation, Mao and coworkers developed a CAIX-anchored benzene sulfonamide

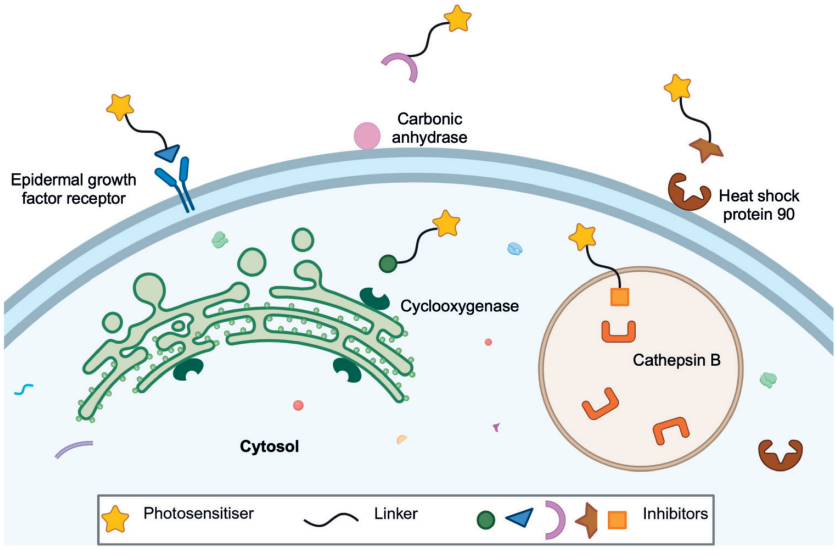


Fig. 2. Schematic overview of key intracellular and extracellular targets for directed photodynamic therapy through enzyme inhibition. Targeted delivery of photosensitisers to overexpressed enzymes such as COX, CA, Cathepsin B, EGFR, or Hsp90.

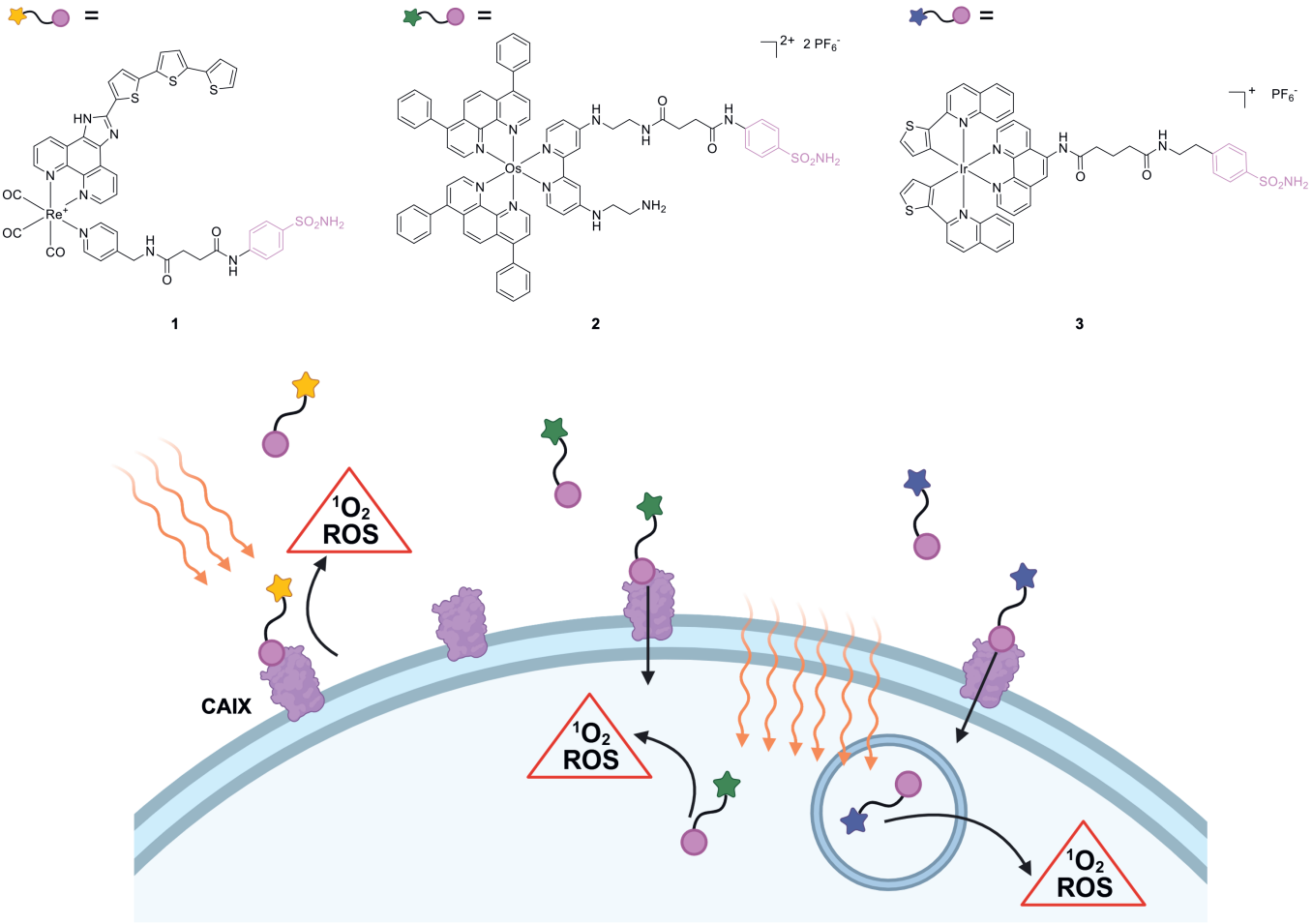


Fig. 3. Schematic representation of CAIX targeted PDT. Photosensitisers **1–3** each incorporate a benzylsulfonamide moiety (highlighted as purple dots) to enable selective CAIX binding. PDT activation occurs upon irradiation at their respective absorption wavelengths (**1**: 425 nm, **2**: 740 nm, **3**: 425 nm), corresponding to the metal-to-ligand charge transfer (MLCT) bands of the metal centre.

rhenium(I) PS designed to enhance tumour immunogenicity (Fig. 3, **1**).[39] Whereas conventional PDT mainly induces apoptosis, which eliminates tumour cells without triggering immune activation, this approach aimed to provoke pyroptosis, a pro-inflammatory form of cell death that amplifies anti-tumour immunity.[40] The CAIX-conjugated PS accumulates in the tumour cell membrane, where PDT-generated ROS (after irradiation at 425 nm) activate pyroptotic signalling, leading to pore formation, osmotic collapse, and release of antigens and damage-associated molecular patterns (DAMPs). These danger signals convert the tumour from 'cold' to 'hot', thereby promoting T-cell infiltration. In parallel, ICB lifts tumour-imposed inhibitory signals, enabling T cells to effectively recognise and attack malignant cells. This effect is also referred to as immunogenic photodynamic therapy (IPDT), which has recently gained attention due to its ability to induce a so-called 'anti-cancer vaccination effect' and thereby trigger a systemic immune response following a localised cancer treatment. By engaging the immune system, IPDT may serve as a mechanistic basis for the abscopal effect, enabling the immune-mediated destruction of distant tumours in response to localised immunogenic cell death (ICD).[41]

As highlighted in the introduction, most metal-based PSs, commonly those incorporating ruthenium, predominantly absorb in the range 400–650 nm.[42,43] To address this limitation, Gasser and coworkers developed four Ru(II)/Os(II)-based photosensitisers incorporating a benzene sulfonamide CA inhibitor (Fig. 3, **2**).[44] The incorporation of osmium, compared to ruthenium, induced a pronounced red-shift of the absorption spectrum, enabling deep-red-PDT application (at 740 nm). The metal complexes exhibited good stability in cellular medium and effectively inhibited tumour-associated CAIX, while retaining residual activity against CAII. They also demonstrated significant phototoxicity under both hypoxic and normoxic conditions. Notably, the Os(II) PSs preserved higher phototoxicity under hypoxia than their Ru(II) counterparts, owing to their ability to switch from Type II to Type I ROS generation, thereby mitigating one of the key limitations of oxygen-dependent PDT.

The reduced efficacy of many PSs in hypoxic tissues can be mitigated by Ir(III)-based complexes, which exhibit strong ROS generation and are therefore of particular relevance for oxygen-independent PDT.[45] Yang and coworkers developed two phosphorescent Ir(III)-based PSs functionalised with benzene sulfonamide-derived CAIX inhibitors (Fig. 3, **3**).[46] These metal complexes display potent CAIX inhibition and preferential accumulation in cancer cells, while the conjugated CAIX-inhibitor moiety decreases their intrinsic dark toxicity towards normal cells, thereby enhancing tumour-selective cytotoxicity. Upon lysosomal accumulation, PDT activation upon 425 nm irradiation induces mitochondrial dysfunction, ultimately resulting in apoptosis.

In summary, these studies highlight the versatility of CAIX-targeted metal-based PSs and collectively position this approach as a highly promising strategy for achieving selective tumour eradication.

3. Cathepsin B

Cathepsin B (CTSB), one of 15 known cathepsin proteases, is classified as a cysteine protease and implicated in the degrada-

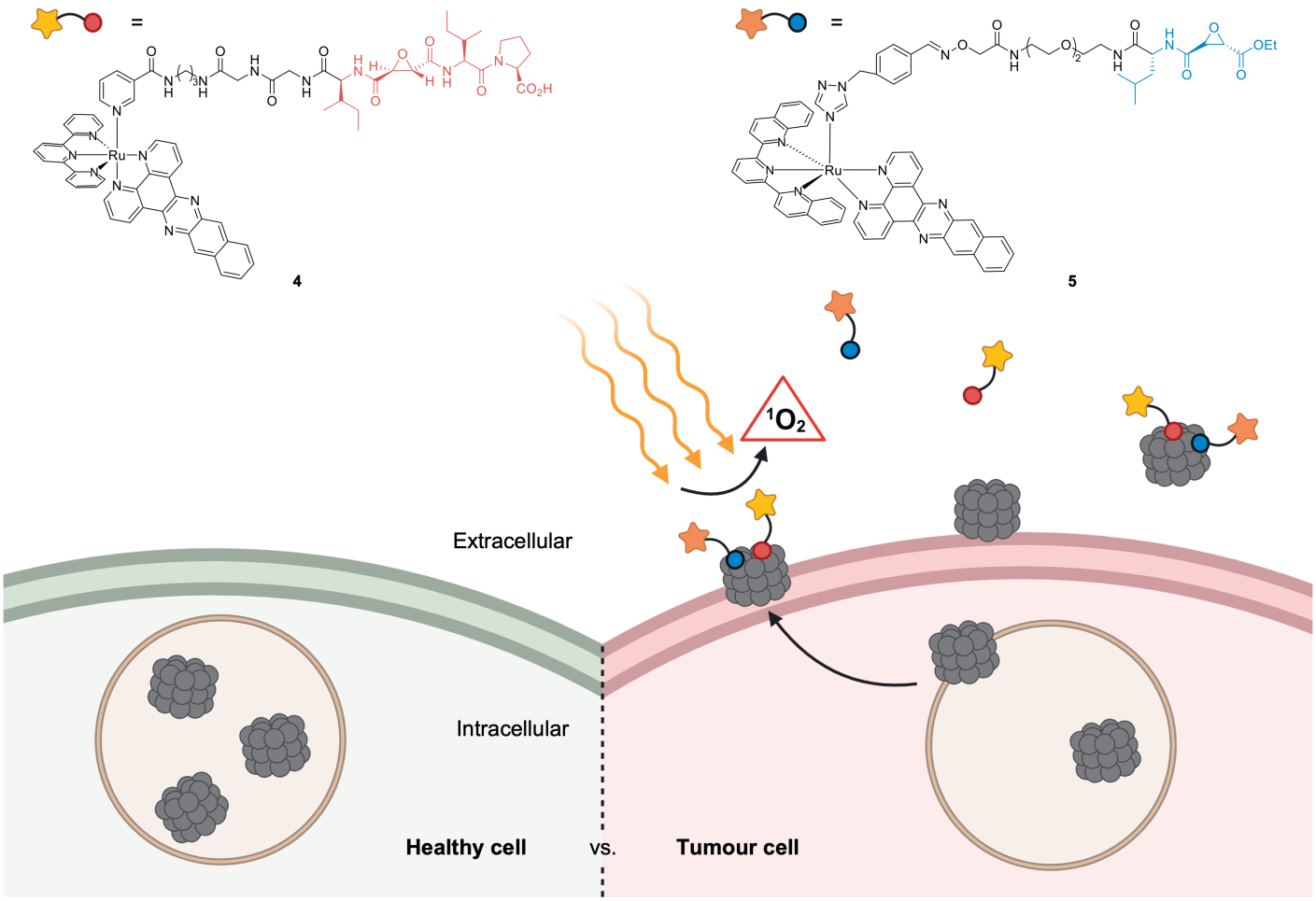


Fig. 4. Schematic representation cathepsin B-targeted PSs. Irreversible binding of **7** and **9** to cathepsin B epoxysuccinyl moiety. PDT activation occurs upon irradiation at their respective absorption wavelengths (**4**: 482 nm, **5**: 525 nm).

tion of intracellular and extracellular proteins. CTSB is normally localised within the lysosomes of healthy cells, where the acidic pH ensures maximal enzymatic activity. In cancer cells, energy metabolism is reprogrammed compared to normal cells (Warburg effect), resulting in acidification of the extracellular environment. CTSB is frequently overexpressed and can be released from lysosomes into this acidic medium. As a result, CTSB serves as a biomarker for aggressive tumours and represents a promising target for selective therapeutic approaches.[47] One such approach is the enzymatic inhibition of cathepsin B, which may offer clinical benefit, owing to the functional role of cathepsins in degrading extracellular matrix and thereby promoting cancer invasion and metastasis.[48] Several inhibitors of CTSB have been identified, with CA-074 and E64d standing out as particularly potent epoxysuccinyl based examples (Scheme 1).[49]

Their inhibitory binding mode relies on a cysteine residue present in the active site, which triggers epoxide ring opening. The resulting thioether represents the covalent inhibition product (represented as coloured dots in Fig. 4).[50] Based on these two covalent inhibitors, the following section presents several PSs that have been conjugated to them, thereby enabling tumour-specific PDT activity.

Scheme 1. Cathepsin B inhibitors CA-074Me and E64d.

Kodanko and coworkers designed and synthesised a series of Ru(II)-based PSs conjugated to a CA-074-derived inhibitor, which are photostable, water-soluble, and cell-permeable. Upon light irradiation, these conjugates induce cell death while simultaneously inhibiting the enzymatic activity of CTSB (Fig. 4).[51] The most potent PS of the series was **4** (see Fig. 4), which was able to irreversibly inhibit CTSB and underwent photoactivated ligand dissociation. After absorbing light at 482 nm, singlet oxygen was generated and exhibited sufficient cytotoxicity to induce cell death.

Considering the limitation of the PS's absorption outside the phototherapeutic window, the strategy was refined, and a new generation of PSs conjugated to CTSB inhibitors was developed by the same group.[52] They prepared a ruthenium complex (complex **9**, Fig. 4) bearing two different polypyridyl ligands, in which the π-extended tridentate ligand induces a red-shift in the absorption profile. Exhibiting both PDT and photoactivated chemotherapy (PACT, mediated *via* photoinduced release of the photolabile inhibitor) activity, **5** could be photoactivated by green light (525 nm), and demonstrated a high toxicity under light in the micromolar range while having low dark toxicity, resulting in a phototherapeutic index (PI, the ratio of IC_{50}(dark)/IC_{50}(light)) of up to 20, depending on the cell line. Crucially, these conjugates show reduced dark toxicity and potent effects against both breast cancer cells and tumour-associated macrophages, highlighting their potential not only as anti-invasive PDT agents but also as modulators of the immunosuppressive tumour microenvironment. These studies illustrate the progression from proof-of-concept CTSB-targeted PSs towards more translatable, dual-action conjugates that exploit both enzymatic inhibition and photoactivation for targeted cancer therapy. Potential immuno-

genic responses *in vivo* hold promises for harnessing the benefits of IPDT but are yet to be demonstrated *in vivo*.

4. Cyclooxygenase (COX)

Cyclooxygenases are a class of enzymes that play a central role in the body's inflammatory response. They are part of the eicosanoid biosynthetic pathway and are responsible for the conversion of arachidonic acid (a fatty acid) into prostaglandins, thromboxanes, and other signalling molecules. Two isoforms of COX have been well-characterised in humans. COX-1 is recognised as the 'constitutive isoform', maintaining cellular homeostasis, whereas COX-2 is canonically inducible and facilitates signalling pathways that regulate cell growth and differentiation.[53] COX enzymes are the targets of several analgesic drugs, which inhibit COX-1 and/or COX-2 either selectively or non-selectively. Beyond the non-selective COX inhibitors like acetylsalicylic acid (aspirin) and indomethacin, selective COX-2 inhibitors like celecoxib and rofecoxib have attracted considerable interest not only in the treatment of pain and inflammation, but also in cancer research.[54] COX-2 is overexpressed in a variety of human cancers including colorectal adenomas and carcinomas, and distinctly not observed in healthy epithelium. Furthermore, inhibition of COX-2 selectively in tumours can be clinically beneficial by reducing the progression of cancer.[55] The conjugation of a PS to a COX-2 inhibitor therefore holds great potential for tPDT. Ideally, the bimodal mechanism of action for COX-2 inhibitor-conjugated PSs should improve anticancer properties whilst minimising side effects associated with systemic COX-2 inhibition.[54] The following section presents three examples based on the conjugation of a PS to a small-molecule COX inhibitor. Two of these molecules were designed using the COX-2 selective inhibitor, celecoxib, whilst a third one employed the nonselective COX inhibitor indomethacin (Scheme 2).

Scheme 2. Cyclooxygenase inhibitors Celecoxib and Indomethacin.

Celecoxib binds selectively to the active site of COX-2, engaging in a combination of hydrophobic and electrostatic interactions. Its *para*-sulfonamide group penetrates deeply into the enzyme's secondary pocket, forming strong interactions with the surrounding amino acid residues. In contrast, indomethacin anchors to the Arg120 side chain *via* ionic interactions through its carboxyl group, while its hydrophobic moiety associates with the non-polar regions of the active site.[54]

Kim and coworkers characterised a lutetium texaphyrin–celecoxib conjugate (**LuCXB**, Fig. 5), which exhibits deep-red absorption at 730 nm.[56] The **LuCXB** absorption characteristics differ depending on the solvent environment, which consequen-

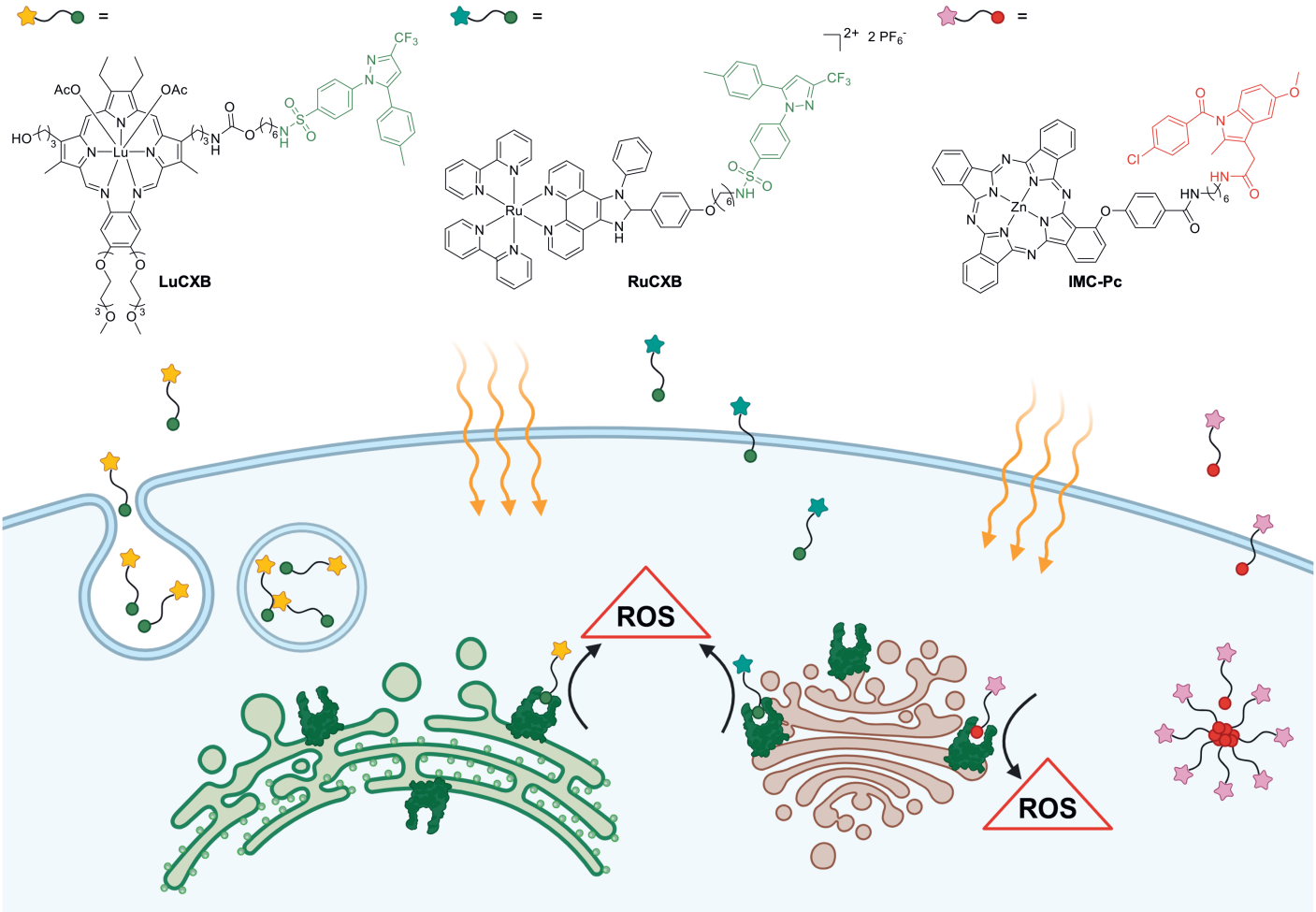


Fig. 5. Schematic representation of cyclooxygenase 2 (COX-2)-targeted PSs. RuCXB, LuCXB and IMC-Pc bind COX-2 *via* either a celecoxib or indomethacin moiety. PDT activation occurs upon irradiation at their respective absorption wavelengths (**LuCXB**: 730 nm, **RuCXB**: 460 nm, **IMC-Pc**: 674 nm).

tially affects the photodynamic pathways it can undertake. In aqueous environments, donor–acceptor interactions resulting from π–π stacking between the texaphyrin PS and the celecoxib inhibitor promote superoxide generation *via* a type I photodynamic mechanism. The type I photodynamic mechanism is tailored towards the hypoxic environment of tumours, owing to efficient production of ROS. In non-aqueous media, the donor–acceptor interaction becomes negligible, leading to a shift towards a type II mechanism. **LuCXB** demonstrated two primary modes of action: an anti-tumour immune response following immunogenic cell death (ICD), whilst also inhibiting pro-angiogenic pathways *via* enzymatic COX-2 inhibition. The ability of **LuCXB** to induce immunogenic cell death positions it as a promising candidate for IPDT. By counteracting tumour immune escape mechanisms, such approaches may significantly enhance the therapeutic efficacy of PDT.

Guo and coworkers simultaneously synthesised another celecoxib-conjugated PS (**RuCXB**, Fig. 5). It exhibits reduced oxygen dependence and, by operating through a type I photodynamic mechanism, is well suited to the hypoxic environment of tumours.[57] The PS localises specifically to the Golgi apparatus and absorbs light at 460 nm. Upon illumination, it leads to downregulation of COX-2 expression and displays high phototoxicity. Moderate dark toxicity was observed, with PI ranging from 4.8 to 42.2 depending on the cell line. While both **RuCXB** and **LuCXB** are characterised by dual mechanisms of action, **RuCXB** functionally differs from **LuCXB** by inducing ferroptosis as well as apoptosis. Ferroptosis is an immunogenic type of cell death characterised by free iron and lipid peroxidation accumulation.[40] The simultaneous induction of ferroptosis and apoptosis thus offers a promising strategy to overcome tumour hypoxia and resistance to apoptosis, further highlighting the therapeutic potential of a COX-2-targeted type I PS like **RuCXB**.

Distinct from **LuCXB** and **RuCXB** is another COX-targeting PS, but instead of employing celecoxib, an indomethacin moiety (IMC) was conjugated by Chen and collaborators to a zinc phthalocyanine PS (**IMC-Pc**, Fig. 5).[58] **IMC-Pc** was excited at 674 nm, showing phototoxicity in the nanomolar range and nearly no cytotoxic effect in the absence of light. The **IMC-Pc** conjugate exhibits three primary components to its mechanism of action: specificity for COX-2 overexpressing cancer cells, specificity for the Golgi apparatus, and a tendency to disaggregate once bound to the COX-2 enzyme. This unique design circumvents the susceptibility for phthalocyanines to aggregate and consequentially limits non-radiative relaxation pathways that can limit phototherapeutic efficiency.[59] Preferential accumulation in the Golgi reflects the results obtained by the group regarding **LuCXB**, but whether or not **IMC-Pc** results in reduced cellular COX-2 expression is unknown. Together, these COX-targeted PSs exemplify the diversity of rational design strategies that enable selective accumulation, dual-functionality, and effective photodynamic responses even under hypoxic tumour conditions. Their capacity to combine enzyme inhibition with ROS-mediated cytotoxicity and, in some cases, immune activation, positions COX-2 as a valuable molecular gateway for advancing targeted photodynamic cancer therapy.

5. Epidermal Growth Factor Receptor (EGFR)

Tyrosine kinases are enzymes that catalyse the transfer of phosphate groups from adenosine triphosphate (ATP) to tyrosine residues.[60] This phosphorylation alters the activity of the target protein and typically activates signal transduction pathways that regulate cell growth, survival, and differentiation. Tyrosine kinases are frequently overexpressed or mutated in tumours and are often implicated in tumorigenesis, leading to constitutive tyrosine kinase activity and uncontrolled cell proliferation.[61] Consequently, tyrosine kinases represent important targets in cancer therapy, and numerous tyrosine kinase inhibitors (TKIs) are already in clinical use as selective anticancer chemotherapeutics.[62] Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that functions as a transmembrane signalling conduit and is frequently overexpressed or mutated in various human cancers, such as non-small cell lung cancer (NSCLC), glioblastoma, squamous cell carcinoma of the head and neck, breast cancer, colorectal cancer and pancreatic cancer.[63] Among the clinically approved tyrosine kinase inhibitors are erlotinib and vandetanib, both of which reversibly bind to the ATP-binding pocket, thereby inhibiting EGFR autophosphorylation (Scheme 3).

Scheme 3. Tyrosine kinase inhibitors erlotinib and vandetanib.

While erlotinib is a selective EGFR inhibitor, vandetanib acts as a multi-target tyrosine kinase inhibitor.[64] In the following section, several photosensitisers are discussed that target cancer cells through conjugation with an EGFR inhibitor, thereby enabling tumour cell eradication.[65]

Zhdanova and coworkers developed two cationic zinc-arylporphyrin PSs (**6** and **7**, Fig. 6) conjugated to the EGFR tyrosine kinase inhibitor erlotinib.[66] The compounds accumulated in mitochondria, where one derivative is particularly effective in inhibiting EGFR phosphorylation and induced apoptosis. A PI of up to 55 was observed, indicating markedly enhanced cytotoxicity upon irradiation at 420 nm compared to dark conditions. However, the compounds also exhibited considerable intrinsic dark toxicity, a limitation likely exacerbated by the use of Cremophor EL as a solubilising agent, raising concerns about potential side effects on healthy tissues. These findings highlight the potential of EGFR inhibitor-conjugated porphyrins as dual-function agents, yet their substantial dark toxicity underscores the need for structural optimisation and safer delivery systems before clinical translation can be envisioned.

In contrast to these porphyrin–erlotinib conjugates with high dark toxicity, Fedorov and coworkers addressed the issue of poor water solubility through the introduction of a carbohydrate moiety onto a chlorin-e6 PS (molecule **8**, Fig. 6). For tumour targeting, the EGFR inhibitor vandetanib was employed.[67] By incorporating quaternary ammonium cations, the authors achieved improved hydrophilicity and cellular uptake. The conjugates absorbed in the therapeutic window (620 nm), displayed significant phototoxicity, and retained remarkably low dark toxicity (PI~368), while molecular docking and biological assays confirmed EGFR targeting. Building on this concept, they subsequently expanded the approach by systematically varying structural features, including the conjugation pattern, the nature of the central metal ion, and the number of positive charges.[68] Among the developed complexes, an indium-based chlorin-e6 conjugate (**9**, Fig. 6) incorporating a vandetanib-derived EGFR inhibitor demonstrated nanomolar phototoxic activity with a PI exceeding 1000. Owing to its ability to generate both reactive oxygen species and singlet oxygen upon irradiation at 655 nm, it remained active in both oxygen-rich and oxygen-poor regions. Its therapeutic potential was further confirmed by *in vivo* studies.

While the above-described PSs demonstrate notable progress in enhancing solubility, selectivity, and therapeutic indices, their clinical applicability remains limited. A major challenge lies in overcoming tumour resistance and sustaining efficacy in aggressive malignancies such as NSCLC, which has a five-year survival rate of only 15%.[1] Despite the clinical use and ongoing devel-

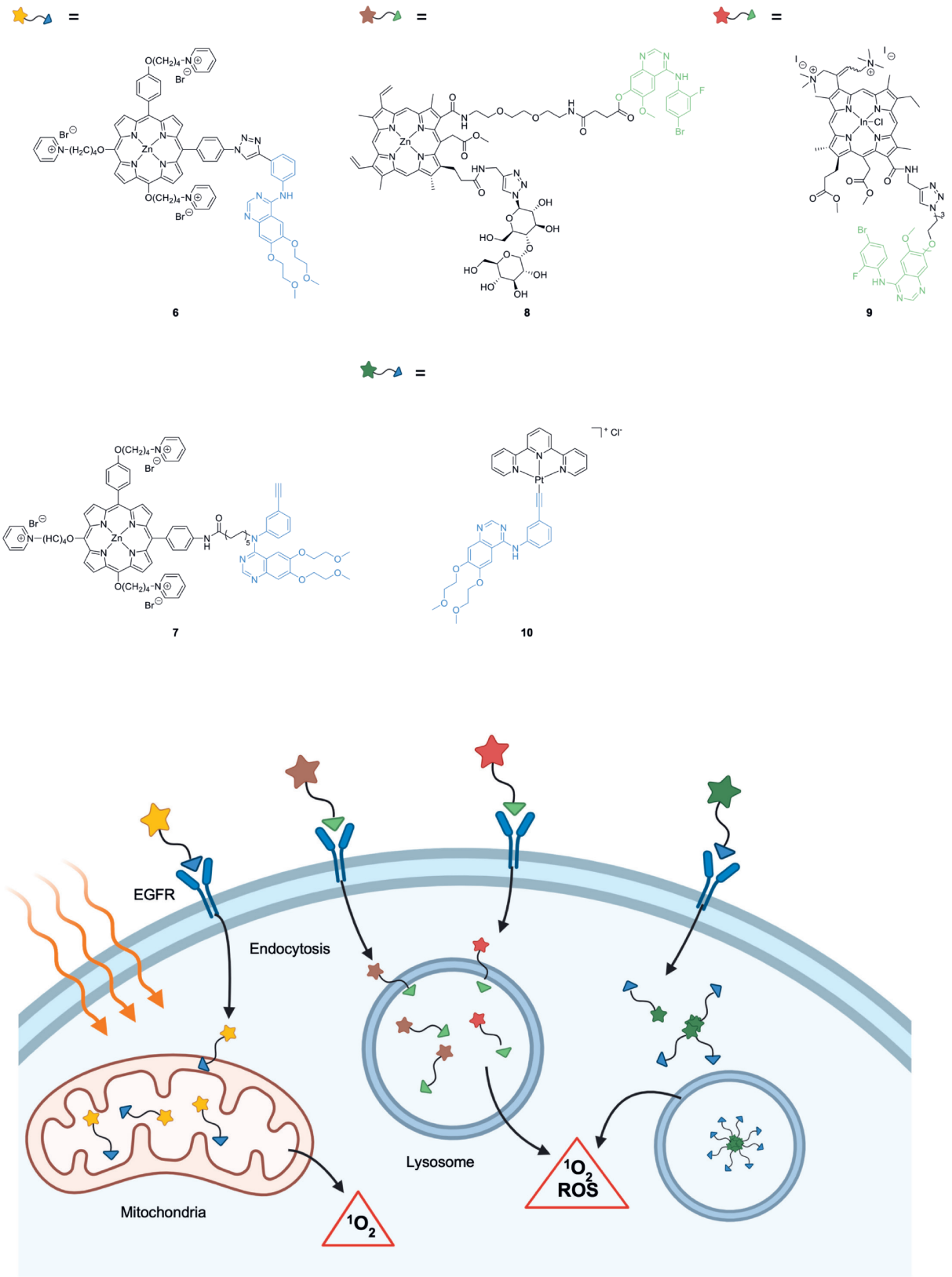


Fig. 6. Accumulation of EGFR-targeted photosensitisers in distinct subcellular compartments depending on structure and linker chemistry. Formation of cytotoxic ROS or singlet oxygen by light activation (**6**, **7**: 420 nm, **8**: 620 nm, **9**: 655 nm, **10**: 465 nm, **11**: 662 nm), leading to targeted tumour cell death.

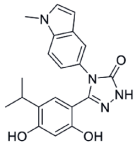
opment of EGFR-targeted TKIs, resistance mutations frequently arise, drastically limiting treatment options.[69,70] To address this, Huang and coworkers developed a platinum(II) pincer complex conjugated with erlotinib as a TKI moiety to achieve selective tumour cell targeting *via* EGFR (**10**, Fig. 6).[71] The complex was shown to self-assemble into nanostructures in aqueous solution, which enhanced both ROS and singlet oxygen generation. Its cytotoxic activity was restricted to EGFR-overexpressing cancer cells (PI from >16 to >63), where EGFR was selectively degraded *via* lysosomal degradation pathways. The metal complexes exhibited

negligible dark toxicity but pronounced light-induced cytotoxicity in the low micromolar range and retained strong activity against cisplatin- and taxol-resistant cell lines. Importantly, their therapeutic efficacy and high biocompatibility were further confirmed in a healthy mouse model.

In summary, EGFR-targeted PSs hold considerable promise for achieving selective tumour ablation by uniting receptor inhibition with photodynamic activation. Although substantial progress has been made in mitigating issues such as dark toxicity, poor solubility, limited selectivity, drug resistance, and inadequate tissue penetration, successful clinical translation will ultimately depend on further optimisation of pharmacokinetic profiles and comprehensive evaluation of long-term safety.

6. Heat Shock Protein 90 (Hsp90)

Heat shock protein 90 (Hsp90) is a molecular chaperone, a protein that assists other proteins in correct folding, activation, and stabilisation. Many oncoproteins are dependent on Hsp90, as they would otherwise undergo rapid degradation.[72] Hsp90 is often overexpressed in tumours, where it promotes survival under stress conditions such as hypoxia or chemotherapy and thereby contributes to tumour progression, metastasis, and therapeutic resistance. Inhibition of Hsp90 results in destabilisation of multiple proteins and the concomitant disruption of several signalling pathways, making it a highly attractive target in cancer research.[73] Several natural and synthetic inhibitors of Hsp90 have been identified, among which Ganetespib (STA-9090), a resorcinol-containing triazolone derivative that targets the *N*-terminal ATP-binding domain of Hsp90, is well known (Scheme 4).[74,75]



Scheme 4. Heat shock protein inhibitor ganetespib.

Building on this, efforts have been made to combine Hsp90 inhibition with photodynamic activation.

Zhao and coworkers reported the first PS covalently conjugated to an Hsp90 inhibitor (**11**, Fig. 7).[76] This Zn–ganetespib conjugate exhibits an absorption maximum at 678 nm, generates reactive oxygen species efficiently, and displays high photostability, all of which are essential features for PDT applications. The conjugate selectively accumulates in cells overexpressing Hsp90 and demonstrated pronounced light-induced cytotoxicity in breast cancer cells. A modest degree of dark toxicity attributable to Hsp90 inhibition was observed, though it remained lower than that of free ganetespib. In mouse models, the PS showed markedly enhanced tumour accumulation and, upon irradiation, achieved near-complete tumour suppression. No significant side effects or body weight loss were detected, underscoring its potential as a highly potent PS for PDT.

7. Conclusion

PDT has been a rapidly evolving cancer treatment for nearly five decades and is already in clinical use or under investigation in clinical trials. However, many PSs still lack sufficient specificity for tumours, which may result in damage to healthy tissue. Consequently, the development of tumour-specific PSs is of considerable interest. Enzymes that are overexpressed in tumours or exclusively present in tumour tissue represent promising targets that can be exploited through selective inhibition. In this review, five distinct proteins with enzymatic activity (CA, Cathepsin B, COX, EGFR, Hsp90) were discussed as targets for tPDT. Metal-based PSs were conjugated to small-molecule enzyme inhibitors *via* a chemical linker, resulting in bifunctional agents that not only enable targeted accumulation within tumour tissue but also modulate pro-tumorigenic signalling pathways. In addition to enzyme inhibition, several strategies were presented to address common limitations of PDT, including tumour hypoxia, absorption outside the phototherapeutic window, poor solubility in biological media, and dark toxicity. In some cases, PDT was successfully combined with ICD or chemotherapeutic mechanisms, further underscoring

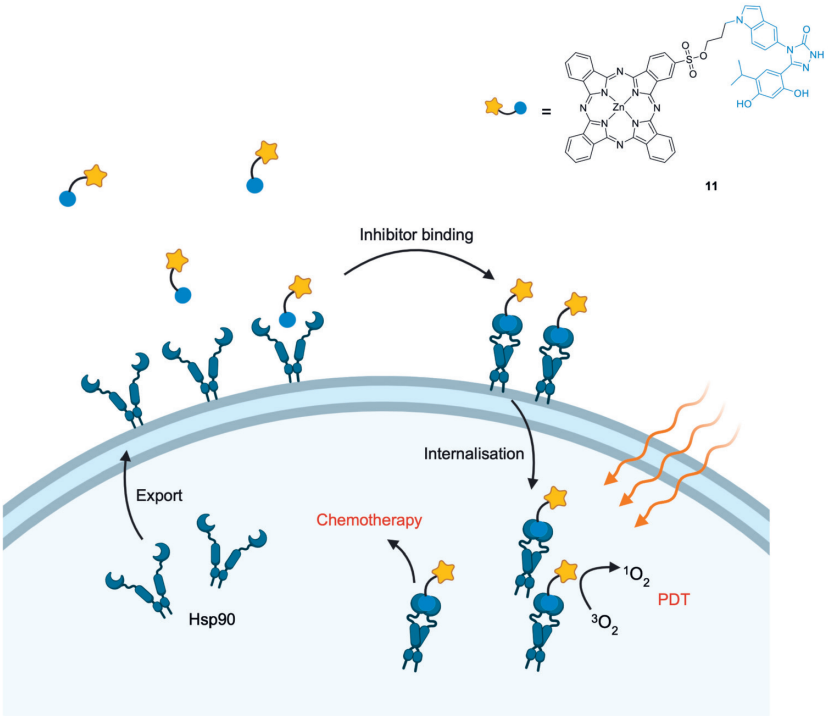


Fig. 7. Hsp90-targeted photosensitisers binding to membrane-associated Hsp90 resulting in intracellular PDT (upon irradiation at 678 nm) and chemotherapy after cellular uptake.

the versatility of this approach. From a translational perspective, such adaptable therapeutic strategies are highly promising within the broader context of precision medicine, as they allow for the rational design of patient-tailored agents based on individual tumour phenotypes. However, tPDT has not yet entered clinical trials. This may be attributed to factors such as the synthetic and formulation complexity of the compounds, suboptimal pharmacokinetic profiles (*e.g.* hydrophobicity, distribution, and clearance), biological limitations (including tumour hypoxia, resistance development, and off-target effects), as well as considerable regulatory requirements and limited industrial interest. tPDT occupies a unique position at the intersection of targeted oncology, photomedicine, and precision therapy. With continued optimisation, it holds strong potential to advance into clinical trials and to serve as a powerful, modular platform for the development of next-generation cancer treatments.

Acknowledgements

This project was funded by the Agence Nationale de la Recherche (ANR) for the project 'OTARI'. J. W. received funding from the School of Chemistry, Monash University, Australia to partially support his stay at Chimie ParisTech.

Graphical Resources

Fig. 1. Created in BioRender. L. Wild, (2025) https://BioRender.com/olkt1ry
Fig. 2. Created in BioRender. L. Wild, (2025) https://BioRender.com/qxc4gyd
Fig. 3. Created in BioRender. L. Wild, (2025) https://BioRender.com/bw58ihp
Fig. 4. Created in BioRender. J. Whitcher, (2025) https://BioRender.com/kcop2q1
Fig. 5. Created in BioRender. J. Whitcher, (2025) https://BioRender.com/shm4w65
Fig. 6. Created in BioRender. L. Wild, (2025) https://BioRender.com/bi7xauj
Fig. 7. Created in BioRender. L. Wild, (2025) https://BioRender.com/c29j8gb

Received: September 30, 2025

[1] H. Sung, J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, *CA-Cancer J. Clin*. **2021**, *71*, 209, https://doi.org/10.3322/caac.21660.
[2] D. E. J. G. J Dolmans, D. Fukumura, R. K. Jain, *Nat. Rev. Cancer* **2003**, *3*, 380, https://doi.org/10.1038/nrc1071T.
[3] T. J. Dougherty, J. E. Kaufman, A. Goldfarb, K. R. Weishaupt, D. Boyle, A. Mittleman, *Cancer Res*. **1978**, *38*, 2628.
[4] J. Karges, *Angew. Chem. Int. Ed*. **2022**, *61*, e202112236, https://doi.org/10.1002/anie.202112236.
[5] L. Benov, *Med. Princ. Pract.* **2014**, *24*, 14, https://doi.org/10.1159/000362416.
[6] L. Chen, Y. Lin, S. Ding, M. Huang, L. Jiang, *Mol. Pharm*aceutics **2025**, *22*, 3530, https://doi.org/10.1021/acs.molpharmaceut.5c00110.
[7] S. A. McFarland, A. Mandel, R. Dumoulin-White, G. Gasser, *Curr. Opin. Chem. Biol*. **2020**, *56*, 23, https://doi.org/10.1016/j.cbpa.2019.10.004.
[8] I. S. Mfouo-Tynga, L.D. Dias, N. M. Inada, C. Kurachi, *Photodiagnosis Photodyn. Ther.* **2021**, *34*, 102091, https://doi.org/10.1016/j.pdpdt.2020.102091.
[9] F. Kradolfer, C. Maake, B. Spingler, *Chem. Commun*. **2025**, *61*, 14757, https://doi.org/10.1039/D5CC02816G.
[10] S. Monro, K. L. Colón, H. Yin, J. I. Roque, P. Konda, S. Gujar, R. P. Thummel, L. Lilge, C. G. Cameron, S. A. McFarland, *Chem. Rev*. **2019**, *119*, 797, https://doi.org/10.1021/acs.chemrev.8b00211.
[11] W. Fan, P. Huang, X. Chen, *Chem. Soc. Rev*. **2016**, *45*, 6488, https://doi.org/10.1039/C6CS00616G
[12] T. C. Pham, V.-N. Nguyen, Y. Choi, S. Lee, J. Yoon, *Chem. Rev*. **2021**, *121*, 13454, https://doi.org/10.1021/acs.chemrev.1c00381.
[13] M. Yu, R. Cao, Z. Ma, M. Zhu, *J. Mater. Chem. B* **2023**, *11*, 1416, https://doi.org/10.1039/D2TB02248F.
[14] X. Zhang, Q. Li, X. Sun, B. Zhang, H. Kang, F. Zhang, Y. Jin, *ACS Biomater. Sci. Eng*. **2017**, *3*, 1008, https://doi.org/10.1021/acsbiomaterials.6b00762.
[15] Z. Wei, X. Liu, D. Niu, L. Qin, Y. Li, *ACS Appl. Bio Mater*. **2020**, *3*, 4655, https://doi.org/10.1021/acsabm.0c00524.
[16] W. Hou, F. Xia, C. S. Alves, X. Qian, Y. Yang, D. Cui, *ACS Appl. Mater. Interfaces* **2016**, *8*, 1447, https://doi.org/10.1021/acsami.5b10772.
[17] J. Wang, Y. Li, J. Zhang, T. Liu, R. Lin, Y. Shan, J. Zhang, *J. Med. Chem*. **2025**, *68*, 17611, https://doi.org/10.1021/acs.jmedchem.5c01296.
[18] H.-X. Zhang, H.-H. Lin, D. Su, D.-C. Yang, J.-Y. Liu, *Mol. Pharm*aceutics **2022**, *19*, 630, https://doi.org/10.1021/acs.molpharmaceut.1c00761.
[19] L. Wei, X. He, D. Zhao, M. Kandawa-Shultz, G. Shao, Y. Wang, *Eur. J. Med. Chem.* **2024**, *264*, 115985, https://doi.org/10.1016/j.ejmech.2023.115985.
[20] A. Bera, A. Nepalia, A. Upadhyay, D. K. Saini, A. R. Chakravarty, *Inorg. Chem*. **2024**, *63*, 17249, https://doi.org/10.1021/acs.inorgchem.4c03083.
[21] S. Zhou, Z. Zhen, A. V. Paschall, L. Xue, X. Yang, A.-G. Bebin Blackwell, Z. Cao, W. Zhang, M. Wang, Y. Teng, G. Zhou, Z. Li, F. Y. Avci, W. Tang, J. Xie, *Adv. Funct. Mater*. **2021**, *31*, 2007017, https://doi.org/10.1002/adfm.202007017.
[22] Q. Wu, C. Yuan, J. Wang, G. Li, C. Zhu, L. Li, Z. Wang, Q. Lv, W. Mei, *JACS Au* **2024**, *4*, 1081, https://doi.org/10.1021/jacsau.3c00808.
[23] G. de F. S. Oliveira, F. S. Gouveia, A. De A. Pinheiro, L. G. Do N. Neto, M. A. de Vasconcelos, E. H. Teixeira, A. C. S. Gondim, L. G. De F. Lopes, I. M. M.de Carvalho, E. H. S. Sousa, *New J. Chem*. **2020**, *44*, 6610, https://doi.org/10.1039/D0NJ00209G.
[24] X. Zhao, M. Li, W. Sun, J. Fan, J. Du, X. Peng, *Chem. Commun*. **2018**, *54*, 7038, https://doi.org/10.1039/C8CC03786H.
[25] J. Sanz-Villafruela, C. Bermejo-Casadesús, G. Riesco-Llach, M. Iglesias, M. Martínez-Alonso, M. Planas, L. Feliu, G. Espino, *Inorg. Chem*. **2024**, *63*, 19140, https://doi.org/10.1021/acs.inorgchem.4c02583.
[26] L. Zhang, P. Wang, X.-Q. Zhou, L. Bretin, X. Zeng, Y. Husiev, E. A. Polanco, G. Zhao, L. S. Wijaya, T. Biver, S. E. Le Dévédec, W. Sun, S. Bonnet, *J. Am. Chem. Soc*. **2023**, *145*, 14963, https://doi.org/10.1021/jacs.3c04855.
[27] H. Zhang, T. Ganguly, R. Harris, R. A. Davis, S. H. Hausner, L. Kovacs, J. L. Sutcliffe, *Bioconjugate Chem*. **2025**, *36*, 1516, https://doi.org/10.1021/acs.bioconjchem.5c00202.
[28] T. Chatzisideri, S. Thysiadis, S. Katsamakas, P. Dalezis, I. Sigala, T. Lazarides, E. Nikolakaki, D. Trafalis, O. A. Gederaas, M. Lindgren, V. Sarli, *Eur. J. Med. Chem*. **2017**, *141*, 221, https://doi.org/10.1016/j.ejmech.2017.09.058.
[29] A. Nguyen, C. Bhandari, M. Keown, A. Malkoochi, M. Quaye, D. Mahmoud, N. Shah, D. Alzhanova, C. G. Cameron, J. Ferruzzi, S. A. McFarland, G. Shafirstein, R. Brekken, G. Obaid, *Mol. Pharm*aceutics **2024**, *21*, 3296, https://doi.org/10.1021/acs.molpharmaceut.4c00046.
[30] J. Jia, Y. Zhang, M. Zheng, C. Shan, H. Yan, W. Wu, X. Gao, B. Cheng, W. Liu, *Inorg. Chem*. **2018**, *57*, 300, https://doi.org/10.1021/acs.inorgchem.7b02475.
[31] Y. Zhao, J. Wang, X. Cai, P. Ding, H. Lv, R. Pei, *ACS Appl. Mater. Interfaces* **2020**, *12*, 23697, https://doi.org/10.1021/acsami.0c04363.
[32] E. Boros, P. J. Dyson, G. Gasser, *Chem* **2020**, *6*, 41, https://doi.org/10.1016/j.chempr.2019.10.013.
[33] G. Gasser, N. Metzler-Nolte, *Curr. Opin. Chem. Biol*. **2012**, *16*, 84, https://doi.org/10.1016/j.cbpa.2012.01.013
[34] P. C. McDonald, J.-Y- Winum, C. T. Supuran, S. Dedhar, *Oncotarget* **2012**, *3*, 84, https://doi.org/10.18632/oncotarget.422.
[35] V. M. Krishnamurthy, G. K. Kaufman, A. R. Urbach, I. Gitlin, K. L. Gudiksen, D. B. Weibel, G. M. Whitesides, *Chem. Rev.* **2008**, *108*, 946, https://doi.org/10.1021/cr050262p.
[36] A. Janoniene, V. Petrikaite, *Mol. Pharmaceutics* **2020**, *17*, 1800, https://doi.org/10.1021/acs.molpharmaceut.0c00180.
[37] K. D'Ambrosio, A. Di Fiore, V. Alterio, E. Langella, S. M. Monti, C. T. Supuran, G. De Simone, *Chem. Rev*. **2025**, *125*, 150, https://doi.org/10.1021/acs.chemrev.4c00278.
[38] V. Alterio, A. Di Fiore, K. D'Ambrosio, C. T. Supuran, G. De Simone, *Chem. Rev*. **2012**, *112*, 4421, https://doi.org/10.1021/cr200176r.
[39] X. Su, W.-J. Wang, Q. Cao, H. Zhang, B. Liu, Y. Ling, X. Zhou, Z.-W. Mao, *Angew. Chem. Int. Ed*. **2022**, *61*, e202115800, https://doi.org/10.1002/anie.202115800.
[40] Y. Zhang, B.-T. Doan, G. Gasser, *Chem. Rev*. **2023**, *123*, 10135, https://doi.org/10.1021/acs.chemrev.3c00161.
[41] Y. Lu, W. Sun, J. Du, J. Fan, X. Peng, *JACS Au* **2023**, *3*, 682, https://doi.org/10.1021/jacsau.2c00591.
[42] H. D. Cole, M. Eroy, J. A. Roque III, G. Shi, M. Guirguis, J. Fakhry, C. G. Cameron, G. Obaid, S. A. McFarland, *Photochem. Photobiol*. **2023**, *99*, 751, https://doi.org/10.1111/php.13756.
[43] J. A. Roque, P. C. Barrett, H. D. Cole, L. M. Lifshits, G. Shi, S. Monro, D. von Dohlen, D. S. Kim, N. Russo, G. Deep, C. G. Cameron, M. E. Alberto, S. A. McFarland, *Chem. Sci*. **2020**, *11*, 9784, https://doi.org/10.1039/D0SC03008B.

[44] Y. Wang, P Mesdom, K. Purkait, B. Saubaméa, P. Burckel, P. Arnoux, C. Frochot, K. Cariou, T. Rossel, G. Gasser, *Chem. Sci.* **2023**, *14*, 11749, https://doi.org/10.1039/D3SC03932C.
[45] C. Liu, Q. Ding, Y. Liu, Z. Wang, Y. Xu, Q. Lu, X. Chen, J. Liu, Y. Sun, R. Li, Y. Yang, Y. Sun, S. Li, P. Wang, P. S. Kim, *Inorg. Chem*. **2024**, *63*, 13059, https://doi.org/10.1021/acs.inorgchem.4c01914.
[46] J. Yang, T. Wang, P. Wang, C. Gao, J. Yang, *Appl. Organomet. Chem*. **2025**, *39*, e7882, https://doi.org/10.1002/aoc.7882.
[47] N. Aggarwal, B. F. Sloane, *Clin. Appl*. **2014**, *8*, 427, https://doi.org/10.1002/prca.201300105.
[48] L. Kramer, D. Turk, B. Turk, *Trends Pharmacol. Sci*. **2017**, *38*, 873, https://doi.org/10.1016/j.tips.2017.06.003.
[49] V. Hook, S. Podvin, M. C. Yoon, V. V. Phan, J. Florio, B. Spencer, C. Mosier, A. Cheng, S. Ahuett, J. Almaliti, W. H. Gerwick, R. A. Rissman, A. J. O'Donoghue, *ACS Chem. Biol.* **2025**, *20*, 1841, https://doi.org/10.1021/acschembio.5c00463.
[50] M. Mladenovic, K. Ansorg, R. F. Fink, W. Thiel, T. Schirmeister, B. Engels, *J. Phys. Chem. B* **2008**, *112*, 11798, https://doi.org/10.1021/jp803895f.
[51] K. Arora, M. Herroon, M. H. Al-Afyouni, N. P. Toupin, T. N. Rohrabaugh, L. M. Loftus, I. Podgorski, C. Turro, J. J. Kodanko, *J. Am. Chem. Soc*. **2018**, *140*, 14367, https://doi.org/10.1021/jacs.8b08853.
[52] M. Denison, S. P. Garcia, A. Ullrich, I. Podgorski, H. Gibson, C. Turro, J. J. Kodanko, *Inorg. Chem*. **2024**, *63*, 7973, https://doi.org/10.1021/acs.inorgchem.4c01008.
[53] C. A. Rouzer, L. J. Marnett, *Chem. Rev*. **2020**, *120*, 7592, https://doi.org/10.1021/acs.chemrev.0c00215.
[54] S. Chahal, P. Rani, Kiran, J. Sindhu, G. Joshi, A. Ganesan, S. Kalyaanamoorthy, Mayank, P. Kumar, R. Singh, A. Negi, *ACS Omega* **2023**, *8*, 17446, https://doi.org/10.1021/acsomega.3c00692.
[55] A. Sahu, K. Raza, D. Pradhan, A. K. Jain, S. Verma, *WIREs Mech. Dis.* **2023**, *15*, e1596, https://doi.org/10.1002/wsbm.1596.
[56] J. An, K.-P. Lv, C. V. Chau, J. H. Lim, R. Parida, X. Huang, S. Debnath, Y. Xu, S. Zheng, A. C. Sedgwick, J. Y. Lee, D. Luo, Q. Liu, J. L. Sessler, J. S. Kim, *J. Am. Chem. Soc*. **2024**, *146*, 19434, https://doi.org/10.1021/jacs.4c05978.
[57] F. Qi, X. Zheng, Y. Wu, S. Li, S. Yao, W. He, Y. Chen, Z. Guo, *Chem. Commun*. **2024**, *60*, 13091, https://doi.org/10.1039/D4CC04217D.
[58] K. Huang, H. Zhang, M. Yan, J. Xue, J. Chen, *Dyes Pigments* **2022**, *198*, 109997, https://doi.org/10.1016/j.dyepig.2021.109997.
[59] L. C. Nene, H. Abrahamse, *Acta Pharm. Sin. B* **2024**, *14*, 1077, https://doi.org/10.1016/j.apsb.2023.11.030.
[60] S. Shaikh, P. S. Chary, N. K. Mehra, *ACS Appl. Bio Mater.* **2025**, *8*, 1749, https://doi.org/10.1021/acsabm.4c01527.
[61] M. K. Paul, A. K. Mukhopadhyay, *Int. J. Med. Sci*. **2004**, *1*, 101, https://doi.org/10.7150/ijms.1.101.
[62] D. F. Beirne, M. Dalla Via, T. Velasco-Torrijos, D. Montagner, *Coord. Chem. Rev*. **2022**, *469*, 214655, https://doi.org/10.1016/j.ccr.2022.214655.
[63] J. K. L. Sinclair, W. E. Robertson, D. Mozumdar, K. Quach, A. Schepartz, *Biochemistry* **2021**, *60*, 500, https://doi.org/10.1021/acs.biochem.0c00978.
[64] A. Tariq, M. Shoaib, L. Qu, S. Shoukat, X. Nan, J. Song, *Eur. J. Pharmacol*. **2025**, *997*, 177608, https://doi.org/10.1016/j.ejphar.2025.177608.
[65] Q. Pan, Y. Lu, L. Xie, D. Wu, R. Liu, W. Gao, K. Luo, B. He, Y. Pu, *Mol. Pharm*. **2023**, *20*, 829, https://doi.org/10.1021/acs.molpharmaceut.2c00792.
[66] Y. S. Bortnevskaya, N. S. Zakharov, V. S. Senkov, M. A. Gradova, N. Y. Karpechenko, E. D. Nikolskaya, M. R. Mollaeva, N. G. Yabbarov, A. S. Novikov, N. A. Bragina, K. A. Zhdanova, *Mol. Pharmaceutics* **2025**, *22*, 3308, https://doi.org/10.1021/acs.molpharmaceut.5c00247.
[67] V. F. Otvagin, N. S. Kuzmina, L. V. Krylova, A. B. Volovetsky, A. V. Nyuchev, A. E. Gavryushin, I. N. Meshkov, Y. G. Gorbunova, Y. V. Romanenko, O. I. Koifman, I. V. Balalaeva, A. Y. Fedorov, *J. Med. Chem*. **2019**, *62*, 11182, https://doi.org/10.1021/acs.jmedchem.9b01294.
[68] L. V. Krylova, V. F. Otvagin, G. P. Gribova, N. S. Kuzmina, E. A. Fedotova, I. V. Zelepukin, A. V. Nyuchev, A. V. Kustov, P. K. Morshnev, D. B. Berezin, M. O. Koifman, S. Z. Vatsadze, I. V. Balalaeva, A. Yu. Fedorov, *J. Med. Chem*. **2025**, *68*, 1901, https://doi.org/10.1021/acs.jmedchem.4c02643.
[69] W. Zhou, D. Ercan, L. Chen, C.-H. Yun, D. Li, M. Capelletti, A. B. Cortot, L. Chirieac, R. E. Lacob, R. Padera, J. R. Engen, K.-K. Wong, M. J. Eck, N. S. Gray, P. A. Jänne, *Nature* **2009**, *462*, 1070, https://doi.org/10.1038/nature08622.
[70] J. P. Robichaux, X. Le, R. S. K. Vijayan, H. K. Hicks, S. Heeke, Y. Y. Elamin, H. Y. Lin, H. Udagawa, F. Skoulidis, H. Tran, S. Varghese, J. He, F. Zhang, M. B. Nilsson, L. Hu, A. Poteete, W. Rinsurongkawong, X Zhang, C Ren, X Liu, L Hong, J. Zhang, L. Diao, R. Madison, A. B. Schrock, J. Saam, V. Raymond, B. Fang, J. Wang, M. J. Ha, J. B. Cross, J. E. Gray, J. V. Heymach, *Nature* **2021**, *597*, 732, https://doi.org/10.1038/s41586-021-03898-1.
[71] H. Wang, Y. Lai, D. Li, J. Karges, P. Zhang, H. Huang, *J. Med. Chem*. **2024**, *67*, 1336, https://doi.org/10.1021/acs.jmedchem.3c01889.
[72] D. Picard, *Nat. Cell Biol*. **2004**, *6*, 479, https://doi.org/10.1038/ncb0604-479.
[73] M. N. Rahimi, L. K. Buckton, S. S. Zaiter, J. Kho, V. Chan, A. Guo, J. Konesan, S. Kwon, L. K. O. Lam, M. F. Lawler, M. Leong, G. D. Moldovan, D. A. Neale, G. Thornton, S. R. McAlpine, *ACS Med. Chem. Lett.* **2018**, *9*, 73, https://doi.org/10.1021/acsmedchemlett.7b00310.
[74] E. M. Kamel, M. A. M. Ali, A. A. Allam, N. A. Ahmed, F. F. A. Alkhayl, A. M. Lamsabhi, *RSC Adv*. **2025**, *15*, 19376, https://doi.org/10.1039/D5RA03137K.
[75] T. Shimamura, S. A. Perera, K. P. Foley, J. Sang, S. J. Rodig, T. Inoue, L. Chen, D. Li, J. Carretero, Y.-C. Li, P. Sinha, C. D. Carey, C. L. Borgman, J.-P. Jimenez, M. Meyerson, W. Ying, J. Barsoum, K.-K. Wong, G. I. Shapiro, *Clin. Cancer Res.* **2012**, *18*, 4973, https://doi.org/10.1158/1078-0432.CCR-11-2967.
[76] L. Huang, G. Wei, X. Sun, Y. Jiang, Z. Huang, Y. Huang, Y. Shen, X. Xu, Y. Liao, C. Zhao, *Eur. J. Med. Chem*. **2018**, *151*, 294, https://doi.org/10.1016/j.ejmech.2018.03.077.

License and Terms

The definitive version of this article is the electronic one that can be found at https://doi.org/10.2533/chimia.2025.838