frontiers | Frontiers in Chemical Biology

TYPE Original Research
PUBLISHED 14 August 2025
DOI 10.3389/fchbi.2025.1620562

OPEN ACCESS

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RECEIVED 29 April 2025
ACCEPTED 29 July 2025
PUBLISHED 14 August 2025

CITATION
Condon C, Careta-Borràs O, Fodor J, Al Riyami AB, Xiao X, Zhao J, Nogués C and Draper SM (2025) Preliminary investigation of Ru(II) complexes bearing nile red chromophores for photodynamic therapy. *Front. Chem. Biol.* 4:1620562. doi: 10.3389/fchbi.2025.1620562

Preliminary investigation of Ru(II) complexes bearing nile red chromophores for photodynamic therapy

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Two previously investigated Ru(II) triplet photosensitisers (PS) (**[Ru-2ENR][$(PF_6)_2$]** and **[Ru-3ENR][$(PF_6)_2$]**) comprising a bipyridyl frame and acetylene appended Nile red chromophore, were converted to their chloride salts for cytotoxicity and phototoxicity measurements. SKBR3-cell lines were used to evaluate the photodynamic activity of the compounds. Irradiation (λ_{ex} 630 nm; 15 min; 33 J cm^{-2}) at a non-toxic concentration of 10 nM, **[Ru-2ENR][$(PF_6)_2$]** and **[Ru-3ENR][$(PF_6)_2$]** induced a reduction in metabolic activity by 60% and 30% respectively.

KEYWORDS

ruthenium, coordination chemistry, photobiology, SKBR-3 breast cancer cells, photodynamic therapy, Nile red

Introduction

Our group previously reported efficient Ru(II) and Ir(III) triplet photosensitisers (PS) when functionalised with pyrene, BODIPY, carbazole, courmarin-6, and Nile red chromophores, in mono- and dinuclear complexes, and in multinuclear porphyrin-based compounds (Conway-Kenny et al., 2021; Cabrera-González et al., 2019; Hallen et al., 2023; Lu et al., 2017; Lu et al., 2018; Lu et al., 2016a; Wang et al., 2018; Wang et al., 2016; Lu et al., 2016b). The purpose of this new work is to evaluate the PS efficiency of the Nile red systems more thoroughly and to explore whether their photophysical properties, which are determined by their structural and electronic features, change when tested in conditions more closely aligned to those used in Photodynamic Therapy (PDT) applications.

Transition metal (TM) polypyridyl compounds benefit from the heavy atom effect. This increases spin orbit coupling and leads to the greater intersystem crossing from the singlet to triplet state, so essential to PDT applications (Josefsen and Boyle, 2008). Metal-polypyridyl frameworks offer diversity and tunability of the photophysical properties; through changing the metal centre or ligand, extending the aromaticity/conjugation of the coordinating ligands and/or attaching chromophores. In particular, Ru(II) complexes often have favourable properties for PDT, such as low dark toxicity and biocompatibility (Mital and Ziora, 2018). TM complexes for PDT are widely explored in the literature (Huang et al., 2019; Mani et al., 2023; Wang et al., 2023; Lazic et al., 2017; Parella et al., 2024), and TLD-

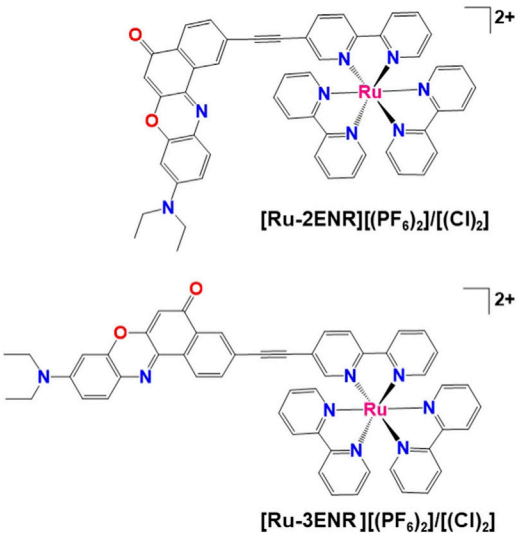

FIGURE 1
Structure of **[Ru-2ENR]**$^{2+}$ and **[Ru-3ENR]**$^{2+}$.

1433, a Ru(II) PS, is currently in clinical trials as a photosensitiser for bladder cancer treatment (Chamberlain et al., 2020; Monro et al., 2019). Evaluating the features of the molecules from a modular approach to PS design, has potential benefits to a wide range of applications.

[Ru-2ENR][(PF$_6$)$_2$] and **[Ru-3ENR][(PF$_6$)$_2$]** (Figure 1) have a Ru(II) bipyridyl frame with an appended Nile red chromophore. The latter is connected to the complex by an acetylene linker, as is characteristic of our group's molecular design motif. The complexes were formed utilising an 'on the complex' synthetic strategy involving Sonogashira coupling reaction (Conway-Kenny et al., 2021; Cabrera-González et al., 2019; Lu et al., 2016a; Condon et al., 2021). Both compounds were shown to absorb strongly in the visible region, with the **[Ru-2ENR][(PF$_6$)$_2$]** ($\varepsilon_{450/557\ nm}$ = 11,900/33,500 M^{-1} cm^{-1}) having reduced molar extinction coefficient compared to **[Ru-3ENR][(PF$_6$)$_2$]** ($\varepsilon_{450/560\ nm}$ = 12,600/47,300 M^{-1} cm^{-1}). Both complexes have two weakly emissive states originating from an intraligand charge transfer, ^{1}ILCT* (557/565 nm), and a metal to ligand charge transfer, ^{3}MLCT* (450 nm) transition. A long lived, ILCT based, non-emissive triplet excited state was also identified (λ_{ex} 510 nm, CH_3CN, [10^{-5} M] **[Ru-2ENR][(PF$_6$)$_2$]**: τ_T 101.4 μs; **[Ru-3ENR][(PF$_6$)$_2$]**: τ_T 266.8 μs) that is capable of significant $^1O_2$ generation (CH_3CN, λ_{ex} 534 nm **[Ru-2ENR][(PF$_6$)$_2$]**: Φ_Δ 42.3%; **[Ru-3ENR][(PF$_6$)$_2$]**: Φ_Δ 51.0%).

Further to our previous work on **[Ru-2ENR][(PF$_6$)$_2$]** and **[Ru-3ENR][(PF$_6$)$_2$]** (Condon et al., 2021), recent computational reports by Scolotti and Mazzone et al. have used these two PF_6 Ru complexes as benchmarks for proposing, via computational analyses, new and analogous compounds for PDT (Barretta et al., 2024a; Barretta et al., 2024b). Their theoretical calculations were in good agreement with our own previously reported computational and photophysical studies. The lowest energy absorptions, assigned as ILCTs in the calculated spectra of **[Ru-2ENR][(PF$_6$)$_2$]** and **[Ru-3ENR][(PF$_6$)$_2$]** were at 561 and 571 nm respectively (557 and 565 nm experimentally). The triplet states reside on the chromophore in both compounds and are ILCT in origin. They are localised on the ethynyl-Nile red moiety for **[Ru-2ENR][(PF$_6$)$_2$]** but extend to include the pyridyl ring on the appended bpy in **[Ru-3ENR][(PF$_6$)$_2$]** as this is the more linear and conjugated of the two ligands.

Computationally determined rate constants of the intersystem crossing, k_{ISC}, for the most plausible ISC process, indicated how well the complexes might populate their triplet excited states. While concluding that both complexes can generate $^1O_2$, **[Ru-2ENR][(PF$_6$)$_2$]** with the lower k_{ISC}, was computationally predicted to have lower efficiency or lower singlet oxygen quantum yields (Barretta et al., 2024a; Barretta et al., 2024b).

Based on the experimental and computational photophysical results, we were encouraged to undertake a preliminary biological evaluation of these two PSs to experimentally determine their potential in solvents and conditions more aligned to those appropriate to photodynamic therapeutic agents and to compare our findings with those anticipated computationally.

Firstly, to further explore the two emissive excited states, nanosecond time-resolved absorption studies were carried out, exciting into the MLCT (450 nm) and the ILCT bands (560 nm) respectively (Supplementary Figures S1, S2). Significant bleaching was observed at circa 560 nm in both complexes due to the depletion of the ground state in the Nile red moiety when exciting at 450 or 560 nm, with the longer wavelength causing considerably greater bleaching. The triplet excited lifetimes (τ_T) at the bleaching peaks were 123.4/140.2 μs for **[Ru-2ENR][(PF$_6$)$_2$]**, (Supplementary Figures S1b,d) and 206.0/234.7 μs for **[Ru-3ENR][(PF6)$_2$]** (Supplementary Figures S2b,d).

The Φ_Δ measurements for the two **[Ru(II)][(PF$_6$)$_2$]** complexes were repeated at a longer excitation wavelength of 610 nm (λ_{ex} = 534 nm previously) in order to approach that of the biological window (650–800 nm) for PDT (Supplementary Figure S3). The Φ_Δ increased by circa 80% for both complexes when excited at a lower energy wavelength with **[Ru-3ENR][(PF$_6$)$_2$]** reaching 90%. The results of the new photophysical measurements are summarised in Table 1.

To improve the solubility of the complexes in aqueous media, their counterions were exchanged for chloride ions by passing them through a short silica column (CH_3CN, H_2O, KCl(aq), 100:10:1 v/v/v). Complete anion exchange was confirmed via ^{35}Cl and ^{19}F NMR spectra (Supplementary Figures S4, S5). It was shown previously that the ^{1}ILCT absorption bands of the complexes were sensitive to the solvent environment and the absorption maxima red-shifted in methanol relative to the spectra in acetonitrile (MeCN) (Condon et al., 2021). The UV-Vis spectra of the chloride salts were therefore measured in MeCN, DMSO and water (Figures 2a,b). As for the PF_6 salts, the ILCT absorption maxima for both Cl compounds are considerably affected showing positive solvatochromism, and significant red shifts in the more polar DMSO and water. Broadened red-shifted absorption bands can be indicative of increased molecular/solvent interactions and the substantial effect of the electronic environment confirms the charge transfer character of this transition. The wavelength of the MLCT absorption maxima are unaffected for **[Ru-2ENR][(Cl)$_2$]** and only slight variation is seen in the extinction coefficient of this band for **[Ru-3ENR][(Cl)$_2$]**.

In water, the ILCT λ_{max} is extended further than 600 nm, shifting by 53 nm for **[Ru-2ENR][(Cl)$_2$]** and 47 nm for **[Ru-3ENR][(Cl)$_2$]** (Figure 2d). The broadened low energy absorption bands now extend to 700 nm, allowing excitation into the desired window for biological applications (650–800 nm). The two Cl compounds in acetonitrile have significantly lower molar extinction coefficients (14,500 and 28,400 M^{-1} cm^{-1}) compared to the PF_6 salts measured

TABLE 1 Photophysical data of [Ru-2ENR][$(PF_6)_2$] and [Ru-3ENR][$(PF_6)_2$].

Complex	λ_{abs}[a] [nm]	ε[a](M^{-1} cm^{-1})	τ_T[b] (μs)	τ_T[c] (μs)	Φ_Δ[d] [%]	Φ_Δ[e] [%]
[Ru-2ENR][$(PF_6)_2$]	450/555	11,900/33,500	123.4	140.2	42.3	77.2
[Ru-3ENR][$(PF_6)_2$]	450/565	12,600/47,300	206.0	234.7	51.0	90.4

[a]Absorption maxima and molar absorptivity in CH_3CN [10_{-5} M], 298 K. Triplet state lifetime in deaerated CH_3CN excited at
[b]450 nm and
[c]565 nm. [10−5 M], 298 K. Singlet oxygen quantum yields determined indirectly from the decay rate of DPBF at λ_{abs} with
[d]diiodobodipy as the standard (Φ_D = 83 % in CH_2Cl_2) in CH_3CN, l_{ex} = 534 nm,
[e]methylene blue as the standard (Φ_D = 57 % in CH_2Cl_2) in CH_3CN, l_{ex} = 610 nm.

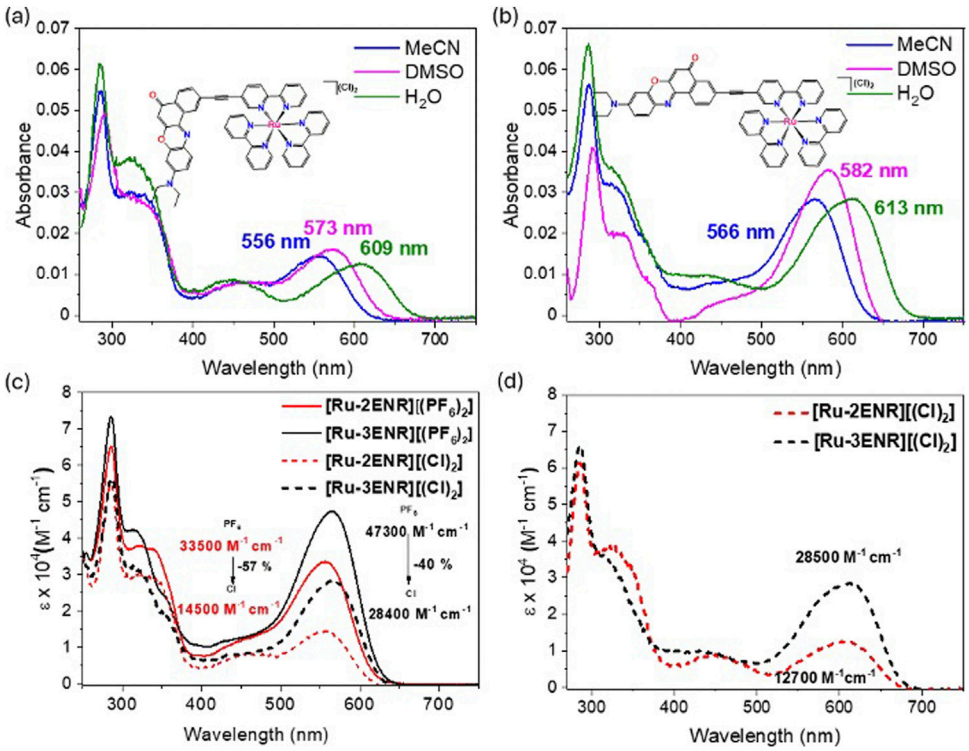

FIGURE 2
UV-visible absorption spectra of **(a) [Ru-2ENR][$(Cl)_2$] (b) [Ru-3ENR][$(Cl)_2$]**, in MeCN, DMSO and H_2O: [10^{-6} M], 298 K. Overlaid UV-visible absorption spectra of **(c) [Ru-2ENR][$(Cl)_2$], [Ru-3ENR][$(Cl)_2$], Ru-2ENR][$(PF_6^-)_2$], [Ru-3ENR][$(PF_6^-)_2$]** in acetonitrile and **(d) [Ru-2ENR][$(Cl)_2$], [Ru-3ENR][$(Cl)_2$]** in water at 298 K.

under the same conditions (Figure 2c), representing a 57% and 40% reduction. However on changing the solvent from MeCN to water for the chloride salts, the molar extinction coefficients of the low energy absorption bands show little change (12,700 and 28,500 M^{-1} cm^{-1}) suggesting that the light-harvesting ability of the chloride salts is not significantly affected by a change in solvent polarity.

Our preliminary biological evaluation began with an investigation of the dark toxicity of **[Ru-2ENR][$(Cl)_2$]** and **[Ru-3ENR][$(Cl)_2$]** using an Alamar Blue assay. This test primarily measures metabolic activity and specifically the redox activity of living cells, which reflects the activity of mitochondrial and cytosolic enzymes. It does not directly measure cell proliferation or growth, but is widely used as a proxy in the literature for cell viability and cytotoxicity due to its sensitivity to changes in cellular metabolic activity.

The dark toxicity of **[Ru-2ENR][$(Cl)_2$]** and **[Ru-3ENR][$(Cl)_2$]** was evaluated using the SKBR-3 cell line (a human breast cancer cell line) to find the concentration at which more than 80% of the cells remain active for the phototoxicity studies. The cells were incubated for 24 h and tested with the Alamar Blue assay (24 h). They were then incubated for another 48 h and a second Alamar Blue assay was performed (72 h) (Supplementary Figure S6). The PSs needed to exhibit less than 20% dark toxicity after 72 h incubation to test for phototoxicity. Between 0.1 and 10 μM concentrations, the toxicity of the compounds was too high and exceeded the maximum 20% (Figure 3; Supplementary Figure S7). Over 80% cell viability was achieved at 0.01 and 0.05 μM for **[Ru-2ENR][$(Cl)_2$]** and 0.01 μM for **[Ru-3ENR][$(Cl)_2$]** (Figures 3a,b).The non-negligible dark toxicity at concentrations in excess of 0.05 μM might be expected to limit the therapeutic application of the materials. To contextualise this information the phototoxicity selectivity indices based on

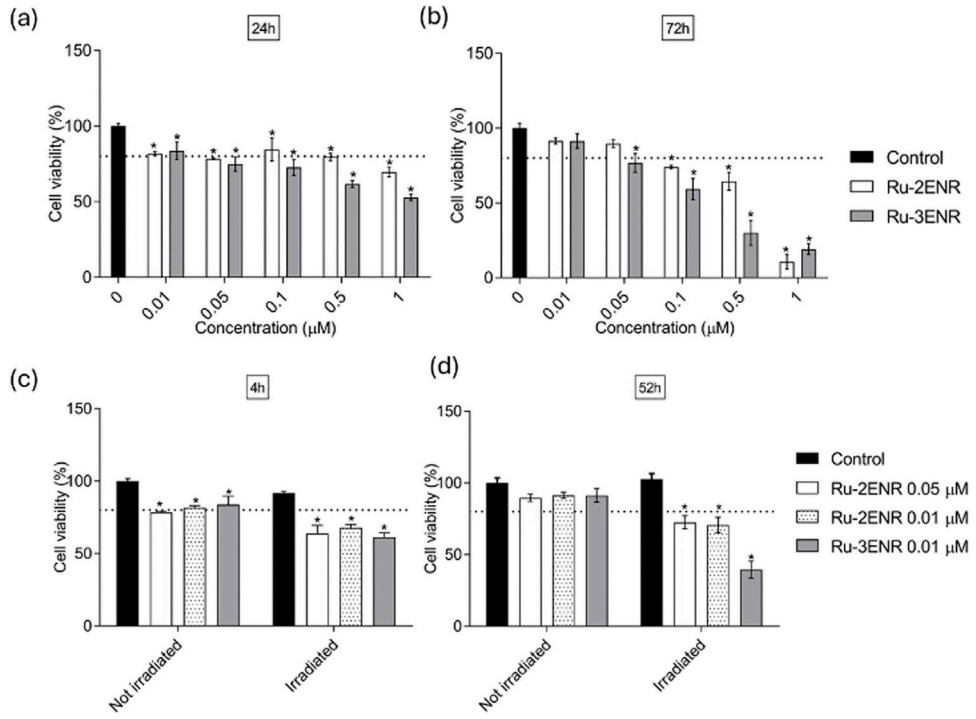

FIGURE 3
Dark toxicity. **(a,b)** Cell viability of SKBR-3 cells incubated in dark conditions with different concentrations of [**Ru-2ENR**][$(Cl)_2$] and [**Ru-3ENR**][$(Cl)_2$], (0.01, 0.05, 0.1, 0.5 and 1 μM), and control (0 μM) at **(a)** 24 h and **(b)** 72 h. Photodynamic treatment effects after 15 min irradiation **(c,d)**. Cell viability of SKBR-3 cells incubated without (control) or with 0.01 and 0.05 μM of [**Ru-2ENR**][$(Cl)_2$] and 0.01 μM of [**Ru-3ENR**][$(Cl)_2$] for 4 h followed by cell wash. Cell viability was determined immediately after incubation **(c)** (4 h) either in dark conditions (not irradiated) or after 15 min irradiation at λ_{ex} 620–630 nm (irradiated) and **(b)** after further 48 h in standard culture conditions (52 h). Three independent experiments were performed for each set of conditions. Asterisks indicate statistically significant differences in the cell viability between the not irradiated control and product at each time-point and condition ($p < 0.05$).

metabolic read-outs from the Alamar Bue Assay are provided (Supplementary Figure S8). The highest selectivity index (2.31) is seen for [**Ru-3ENR**][$(Cl)_2$] at 52h and 0.05 μM.

The phototoxicity of the complexes was tested by irradiating the cells after 4 h incubation with the PSs, at λ_{ex} 630 nm (33 J cm^{-2}) for 15 min. After irradiation, cell viability was tested immediately (4 h, Figure 3c). The cells were then incubated in the dark for 48 h, after which time cell viability was tested again (52 h, Figure 3d). Immediately after irradiation (Figure 3c), a decrease in cell survival was observed for both compounds. After 48 h (Figure 3d), a further decrease in cell viability was also observed. The **3ENR**-appended complex performed better than the **2ENR**. The **3ENR** appended complex showed an increase in Φ_Δ compared to its **2ENR** analogue and had a significantly higher absorption coefficient (55%) in support of the enhanced photodynamic action seen for [**Ru-3ENR**][$(Cl)_2$].

The cellular uptake of the Cl complexes was evaluated by confocal microscopy, at a concentration of 10 μM. The results are presented in Figure 4. For both compounds, most of the PS remained attached to the plasma membrane, with a small amount of the product internalised.

Fluorescence intensity profiles extracted from the confocal images (Supplementary Figure S9) revealed peak intensities at the plasma membrane, consistent with dominant membrane accumulation. Intracellular puncta also displayed localized signals, suggesting vesicular internalization via endocytosis.

Conclusion

[**Ru-2ENR**][$(Cl)_2$] and [**Ru-3ENR**][$(Cl)_2$], two PSs with long excitation wavelengths and excellent singlet oxygen quantum yields (λ_{ex} 610 nm, [**Ru-2ENR**][$(PF_6)_2$], Φ_Δ 77.2%, [**Ru-3ENR**][$(PF_6)_2$], Φ_Δ 90.4%) were evaluated in cell toxicity studies on SKBR-3 cell lines. The cellular uptake of the compounds was minimal with both PSs residing in the plasma membrane. The dark toxicity of the compounds was significant, decreasing viability by 20% at concentrations of 50 nM. The phototoxicity of the compounds (λ_{ex} 630 nm, 33 J cm^{-2}, 15 min) led to circa 30% reduction in the viability for [**Ru-2ENR**][$(Cl)_2$] and about 60% in the case of [**Ru-3ENR**][$(Cl)_2$] at 10–50 nM concentrations. While the efficiency of the PSs is limited by their poor cellular uptake, [**Ru-3ENR**][$(Cl)_2$] still shows good activity at the nanomolar region. The greater linearity of the coordinated 3ENR manifests a change in the degree of electronic delocalisation and the nature of the triplet excited state which is found to be situated across the entirety of the pyridyl-3ENR ligand. This improves the lifetime of the triplet excited state and $^1O_2$ quantum yields as evidenced in similar systems in which the more linear framework shows photophysical improvements and is consistent

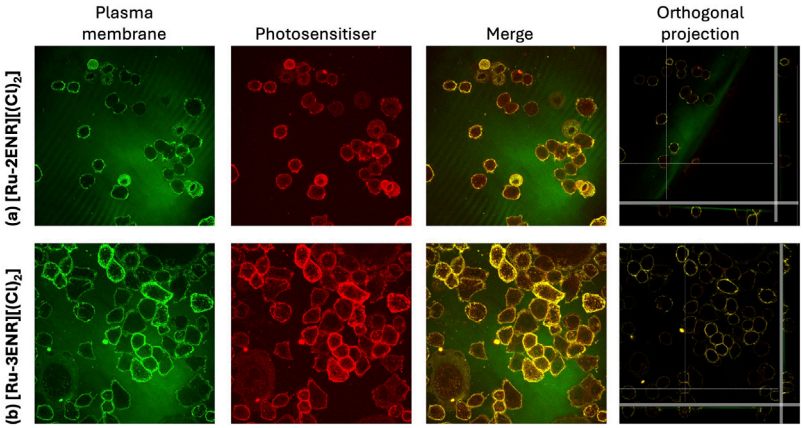

FIGURE 4
Product internalisation. Live SKBR-3 cells incubated with 10 μM of **(a)** [**Ru-2ENR**][$(Cl)_2$], **(b)** [**Ru-3ENR**][$(Cl)_2$], for 4 h and observed under confocal microscope. To analyse the localisation of the product, fluorescence mode was used. Product fluorescence emission was detected in the range of λ_{em} 580–699 nm by exciting the cells using a λ_{ex} 488 nm laser (15% of laser power). Wheat germ agglutinin (WGA) fluorescence emission (membrane) was detected in the range of λ_{em} 500–530 nm (green) by exciting the cells using a λ_{ex} 488 nm laser (12% of laser power). Maximum projection and orthogonal projection of z-stacks. Scale bar, 20 μm.

with the previous computational evaluations (Lazic et al., 2017; Parella et al., 2024; Chamberlain et al., 2020).

Both photophysical measurements and theoretical calculations suggested that [**Ru-3ENR**][$(PF_6)_2$] would be a better performing PS, due to having higher Φ_Δ, higher absorption and a higher rate constant of the intersystem crossing, k_{ISC}. These predictions carried through into the *in vitro* cell studies however experimentally determining the influence of the solvent was important particularly due to the IL* charge transfer nature of the excited state. In addition, the photophysical properties such as absorption, emission, and singlet oxygen quantum yields were found to change significantly and in some cases favourably upon anion exchange (from PF_6 to Cl). The suitability of PS in biological applications such as PDT is also determined by the dark toxicity and cellular uptake. We will direct further studies with a view to exploring analogue modifications of the above complex salts. These will include detailed analyses involving mitochondrial assays, the mechanism of cell death, and the quantification of ROS generation, as appropriate. The aim will be to target improvements in terms of their cellular uptake while retaining the very advantageous photophysical properties of the materials examined to date.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

Ethical approval was not required for the studies on humans in accordance with the local legislation and institutional requirements because only commercially available established cell lines were used.

Author contributions

CC: Investigation, Conceptualization, Writing – review and editing, Software, Methodology, Formal Analysis, Visualization, Data curation, Writing – original draft. OC-B: Writing – original draft, Formal Analysis, Visualization, Data curation, Investigation, Methodology, Writing – review and editing. JF: Writing – original draft, Formal Analysis, Visualization, Writing – review and editing, Data curation. AA: Writing – review and editing, Visualization. XX: Data curation, Methodology, Investigation, Software, Formal Analysis, Writing – review and editing. JZ: Supervision, Writing – review and editing, Resources. CN: Writing – review and editing, Resources, Writing – original draft, Visualization, Formal Analysis, Investigation, Supervision, Methodology. SD: Validation, Resources, Data curation, Conceptualization, Project administration, Formal Analysis, Investigation, Funding acquisition, Methodology, Writing – review and editing, Supervision, Writing – original draft.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This publication has emanated from research conducted with the financial support of Science Foundation Ireland (Grant Number 15/IA/3046), and Research Ireland (Grant Number 12/RC/2278_2) which is co-funded under the European Regional Development Fund under the AMBER award. A.Al-R. acknowledges funding from a TCD Postgraduate Studentship 1252 Award. C.C., and J.F. acknowledge funding support from the Trinity Research Doctoral Higher Education Authority and the Department of Further and Higher Education, Research, Innovation and Science.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchbi.2025.1620562/full#supplementary-material

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