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Authors: Claudia Dragonetti, Alessia Colombo, Mattia Fontani, Dominique Roberto, Gareth Williams, Rossella Scotto di Perrotolo, Francesca Casagrande, Sara Barozzi, and Simona Polo

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A highly luminescent tetrahydrocurcumin Ir(III) complex with remarkable photoactivated anticancer activity

Alessia Colombo,^[a] Mattia Fontani,^[a] Claudia Dragonetti,^{[a]*} Dominique Roberto,^[a] J. A. Gareth Williams,^{[b]*} Rossella Scotto di Perrotolo,^[c] Francesca Casagrande,^[c] Sara Barozzi,^[c] and Simona Polo^{[c],[d]*}

Dedicated to Emeritus Professor Renato Ugo for his 81st birthday

Abstract: Curcumin has chemopreventive properties against a variety of tumours, but it has poor bioavailability. Two new bis-cyclometallated iridium(III) complexes have been prepared, featuring the natural product curcumin (CUR) or its reduced form, tetrahydrocurcumin (THC), as bidentate, anionic *O*[−]*O*-binding ligands. The iridium THC complex is highly luminescent in deoxygenated solution and efficiently generates singlet oxygen under aerated conditions, whereas in the curcumin analogue, other non-radiative decay pathways are competitive. The complexes are rapidly taken up into a variety of human tumour cell lines from solutions of micromolar concentration. They have negligible cytotoxicity in the absence of irradiation. When briefly irradiated by visible light, Ir-THC becomes highly phototoxic, inducing rapid apoptosis within 2 h. The results show the high potential of such complexes as sensitizers in photodynamic therapy (PDT).

8 g / day with no side effects.^[3] However, CUR shows poor oral bioavailability: its concentration in human plasma and other tissues is extremely low even after a high oral dose. This is due to its instability with respect to hydrolysis of the β -diketone unit under physiological conditions, rapidly leading to species such as ferullic acid and vanillin.^[4,5] Interestingly, binding this moiety in the deprotonated anionic form to a metal centre increases its hydrolytic stability, with respect to free curcumin, and the resulting complexes can show cytotoxic activity.^[4,6] Indeed, a bioreductively-activated cobalt(III) carrier system for the delivery of curcumin with enhanced drug stability and efficacy against colon cancer cells was recently reported.^[4b]

Introduction

Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (CUR, Fig. 1), is a polyphenolic natural product isolated from *Curcuma longa*, a rhizomatous herbaceous plant. CUR has been a well-recognized dietary spice for centuries and its pharmacological activities have been studied in various clinical studies including anti-inflammatory, anti-diabetic, anti-dementia, and anti-oxidant properties.^[1] In particular, it appears to have chemopreventive properties against a variety of human malignancies and is currently in clinical trials as an anticancer agent.^[2] In Phase I clinical trials, it was concluded that humans can tolerate a CUR dose as high as

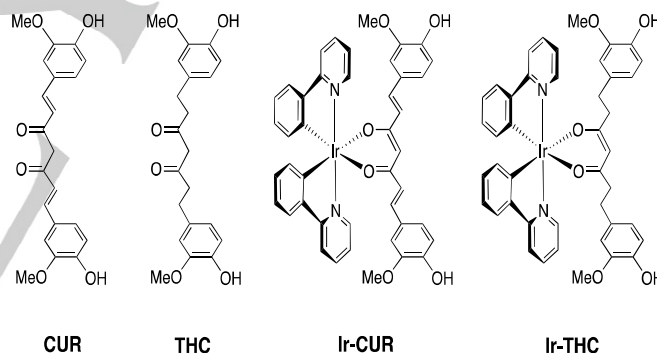


Figure 1. The structures of curcumin (CUR), tetrahydrocurcumin (THC), and their corresponding iridium(III) complexes Ir-CUR and Ir-THC featuring the ligands in their anionic (deprotonated) forms.

The high instability of CUR suggests that it may be the products of its metabolism that are responsible for its pharmacological effects *in vivo*.^[7] In particular, tetrahydrocurcumin (THC) is one of CUR active metabolites (Fig. 1) and might play a crucial role in CUR-induced biological effects. Its easy absorption through the gastrointestinal tract suggests that THC might even be a better candidate than CUR for the development of anticancer agents.^[8] In agreement with this observation, THC exhibits significant cell growth inhibition by inducing human breast cancer MCF-7 cells to undergo mitochondrial apoptosis and G2/M arrest.^[8]

The photobiological activity of curcumin is related to its ability to generate reactive oxygen species (ROS) which

[a] Dr A. Colombo, Dr M. Fontani, Prof. C. Dragonetti, Prof. D. Roberto
Dip. di Chimica dell'Università degli Studi di Milano and UdR INSTM
di Milano, via Golgi 19, 20133 Milano, Italy
E-mail: claudia.dragonetti@unimi.it

[b] Prof. J. A. Gareth Williams
Department of Chemistry
Durham University
Durham, UK

[c] Dr. R. Scotto di Perrotolo, Dr. Casagrande, Dr. Barozzi, Dr. S. Polo
IFOM, Fondazione Istituto FIRC di Oncologia Molecolare,
Via Adamello 16, 20145, Milan, Italy.

[d] Dr. S. Polo
Dipartimento di Oncologia ed Emato-Oncologia,
Università degli Studi di Milano,
20139, Milan, Italy.

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lead to cancer cell death by apoptosis via mitochondrial pathways.^[4] Curcumin's photochemical properties are therefore important in this context.^[9] It shows a strong absorption band around 410–430 nm and fluorescence in the region 460–560 nm in solution at room temperature, with a quantum yield in the range 0.02–0.08 according to the solvent. While the singlet excited state decays by a non-radiative process, its triplet state reacts with ground-state $^3\text{O}_2$ to generate singlet oxygen $^1\text{O}_2$ efficiently. CUR is thus of great interest for photodynamic therapy (PDT), a treatment in which the cytotoxicity of a drug is selectively activated by light only in cancerous regions, through generation of $^1\text{O}_2$, and showing promise for several types of solid cancer.^[10, 11]

Nevertheless, although curcumin could have potential as a PDT agent, its low bioavailability would severely limit its efficacy. The greater stability of metal complexes of CUR, coupled with longer-wavelength absorption, could render them suitable for such phototherapeutic applications.^[4] Surprisingly, despite growing interest in the use of iridium complexes as PDT agents,^[11] only one iridium complex incorporating curcumin as a ligand has been reported up to now.^[12] Pettinari *et al.* reported that $[\text{Cp}^*\text{Ir}(\text{curc})\text{Cl}]$ (in which $\text{Cp}^* = \text{pentamethylcyclopentadienyl}$, $\text{curcH} = \text{curcumin}$) is moderately cytotoxic to both human ovarian cancer cells and non-tumorigenic human embryonic kidney cells, though its potential as a PDT agent was not investigated.^[12b] However, cyclometallated Ir(III) complexes could have great potential in PDT because they may efficiently generate $^1\text{O}_2$ due to the presence of the heavy atom which favours a fast intersystem crossing to triplet states with microsecond lifetimes.^[13] Moreover, they are often luminescent, offering potential for cellular imaging, and for what is known as theranostics – the combination of therapy and imaging.^[14–27] Based on these observations, we decided to prepare and study an Ir(III) complex bearing two cyclometallated phenylpyridine (ppy) ligands and curcumin (Ir-CUR, Fig. 1). We also synthesised the related complex with tetrahydrocurcumin (Ir-THC, Fig. 1), whose metal complexes have never been reported.

Results and Discussion

The target Ir(III) complexes (Fig.1) resemble in structure those of the type $[\text{Ir}(\text{N}^{\wedge}\text{C})_2(\text{O}^{\wedge}\text{O})]$, where $\text{O}^{\wedge}\text{O}$ is an anionic β -diketonate ligand of which acetylacetonate (acac^-) is the archetypal example.^[16] They were synthesised by reaction of $[\text{Ir}(\text{N}^{\wedge}\text{C-ppy})_2(\mu\text{-Cl})_2]$ with the commercial curcumin or tetrahydrocurcumin proligand in methanol in the presence of sodium methoxide to deprotonate the β -diketone (Scheme S1 in the Supporting Information, SI). The desired products were purified by recrystallization from a mixture of dichloromethane and diethylether. The identities and purities of the products were confirmed by ^1H and ^{13}C NMR spectroscopy and by elemental analysis (details are provided in the SI). The UV-visible spectra of the two complexes show moderately intense absorption bands stretching into the visible region due to charge-transfer transitions, along with $\pi\text{--}\pi^*$ bands in

the UV region (Fig. S1, SI). Stability measurements under physiological conditions, both of the ligands and of the iridium complexes, have been performed by monitoring the UV-visible spectra (Fig. S2, SI). The results evidence that curcumin is not stable under physiological conditions, whereas tetrahydrocurcumin and both of the new iridium complexes are rather stable.

At room temperature, the Ir-CUR complex shows no detectable luminescence in deoxygenated CH_2Cl_2 solution. The lack of luminescence would be consistent with a *trans-cis* isomerization of the olefinic double bond acting as a deactivation pathway, as previously suggested in Ir(III) complexes incorporating C=C-appended ligands.^[28,29] It may also be due to the CUR ligand having low-energy π^* orbitals associated with it, such that the lowest-energy triplet excited state becomes localised on this ligand as opposed to it having the usual $\text{d}_{\text{Ir}} / \pi_{\text{ppy}} \rightarrow \pi^*_{\text{ppy}}$ charge-transfer character that would typically lead to efficient phosphorescence. Such an effect is well-established for Ir(III) complexes with $\text{O}^{\wedge}\text{O}$ ligands featuring more extended conjugation, such as dibenzoylmethane, which have low-energy ligand-based triplet-states.^[30] A similar effect has been observed for related platinum(II) complexes with $\text{O}^{\wedge}\text{O}$ ligands featuring low-energy triplet states.^[31] At low temperature (77 K), the deactivating pathway is inhibited: the complex emits in the red region of the spectrum, displaying a highly structured profile, $\lambda_{(0,0)} = 602 \text{ nm}$, and a lifetime of 5.9 μs (spectra are shown in Fig. S1, SI).

In contrast, the related Ir-THC complex, which lacks olefinic bonds in the $\text{O}^{\wedge}\text{O}$ ligand, is an extraordinarily bright green emitter at room temperature ($\lambda_{\text{max}} = 520 \text{ nm}$). The luminescence lifetime is 1.8 μs in deoxygenated CH_2Cl_2 solution whilst its photoluminescence quantum yield of 0.90 renders it one of the most brightly emitting Ir(III) complexes reported, comparable to that of the archetypal complex *fac*- $\text{Ir}(\text{ppy})_3$.^[32] Assuming that the emitting state is formed with unitary efficiency upon light absorption, the radiative rate constant k_r and non-radiative rate constant k_{nr} can be estimated from $k_r = \Phi/\tau$ and $k_{\text{nr}} = (1-\Phi)/\tau$. The high value of k_r of $5 \times 10^5 \text{ s}^{-1}$ coupled with the relatively low value of $5.5 \times 10^4 \text{ s}^{-1}$ for k_{nr} account for the bright emission. This contrasts strikingly with tetrahydrocurcumin itself, which is only very weakly emissive in ethanol solution at room temperature ($\Phi \approx 0.007$).^[33]

The intense green phosphorescence of Ir-THC in deoxygenated solution is strongly quenched by oxygen. The emission lifetime is reduced to 70 ns in air-equilibrated solution, from which a rough estimate of the bimolecular rate constant for quenching by O_2 can be calculated to be $6.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$. Such quenching of transition metal complexes is often accompanied by formation of the excited $^1\Delta_g$ state of oxygen, commonly referred to as singlet oxygen or $^1\text{O}_2$. In the present instance, the emission of the $^1\text{O}_2$ thereby generated could be readily detected in the near infrared (NIR) region (1274 nm; Fig. S1, SI). Using a previously described procedure^[34] with perinaphthenone (also known as phenalenone) as the standard ($\Phi = 0.95$ ^[35]), the quantum yield of $^1\text{O}_2$ generation was estimated to be 0.42 in CH_2Cl_2 . Further details and representative plots are provided in the Supporting Information. As noted above, there is still some phosphorescence observed in air-

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equilibrated solution, and so the singlet oxygen quantum yield under those conditions is somewhat lower than that of phosphorescence in deoxygenated solution. The rate of deactivation of the Ir-THC excited state by oxygen can be estimated from the lifetimes to be around $1.3 \times 10^7 \text{ s}^{-1}$ in air-equilibrated solution which, though larger than the value of k_r given above, still allows some phosphorescence to be observed. No singlet oxygen was detected for Ir-CUR, probably because the rate of deactivation of its triplet state is too fast for it to act as a sensitizer.

The cellular uptake of the new iridium(III) complexes was probed by emission microscopy. Both complexes are characterized by high cell permeability and fast internalization kinetics in A549 – a human alveolar basal epithelial cancer cell line – and in cervical cancer HeLa cells (Fig. 2a and Fig. S3, SI). While the Ir-CUR is barely detectable (as is the case also for controls treated with CUR or THC), the emission from the cells treated with the Ir-THC complex is extremely bright (Fig. 2a). It is visible even after incubation at a dose of $0.3 \mu\text{M}$ and is localized inside the cells at the mitochondria, as confirmed by co-staining experiments with MitoTracker® dyes (Fig. S3, SI).

and 530–560 nm) and for different lengths of time (0.5 s, 1 s and 2 s) and were subsequently monitored over a period of 48 h. As can be seen in Figure S3, A549 cells treated with $30 \mu\text{M}$ of Ir-THC for 2 h in the incubator, and irradiated in the wavelength range 465–495 nm for 2 s (at a power of 5.6 mW mm^{-2}), underwent apoptosis within less than 2 h. The use of light in the 530–560 nm region has an intermediate effect in initiating apoptosis, consistent with the limited absorption of the complexes at such long wavelengths.

Based on the previous observations, we hypothesize that $^1\text{O}_2$ or related reactive oxygen species generated upon excitation of the compound are responsible for the observed phototoxicity. The contrast between the light-induced cytotoxicity and the lack of toxicity in the absence of light is of crucial importance for the design of PDT agents.

To compare Ir-CUR and Ir-THC and confirm the specificity of the cytotoxicity, we performed a series of experiments in which A549 cells were treated with the two complexes and the free pro-ligands CUR and THC at a concentration of $30 \mu\text{M}$ in each case (Fig. 3).

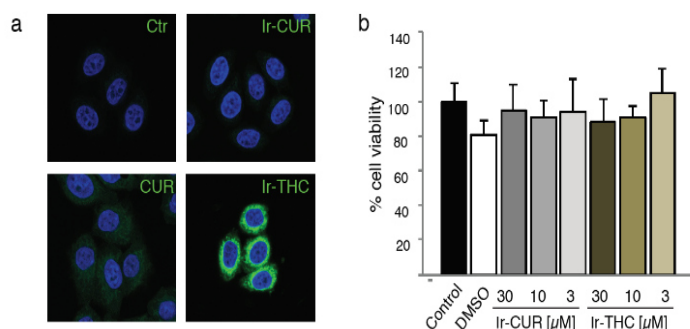


Figure 2 (a) Immunofluorescence analysis of HeLa cells incubated for 2 h with the indicated compounds at $30 \mu\text{M}$ concentration and co-stained with the nucleus-specific dye DAPI. Images were taken by confocal microscopy with an excitation wavelength of 495 nm. Emission from the complexes is green; DAPI is blue and localised to the nuclei. (b) MTT assay of A549 cells continuously treated for 2 days with the indicated concentrations of Ir-CUR and Ir-THC compounds without irradiation. DMSO indicates cells treated with 0.15% DMSO as for the $30 \mu\text{M}$ Ir-Cur and Ir-THC. % of cell viability of the various samples are not statistically different.

It is notable that the cells appear to be unaffected by the presence of the two complexes. This observation was further confirmed by an MTT assay performed at various concentrations of the complexes: no reduction in cell viability was evident, even after 48 h of continuous treatment at concentration of $30 \mu\text{M}$ under normal cell culture conditions (Fig. 2b). These results were further confirmed by a CCK (cell counting kit) assay (Fig. S3c, SI). The photocytotoxicity of the Ir-THC complex was assessed through irradiation at different wavelengths coupled with time-lapse microscopy to view the effect of light on the cells. The cells were irradiated with a xenon lamp through three different excitation filters (360–370 nm, 465–495 nm

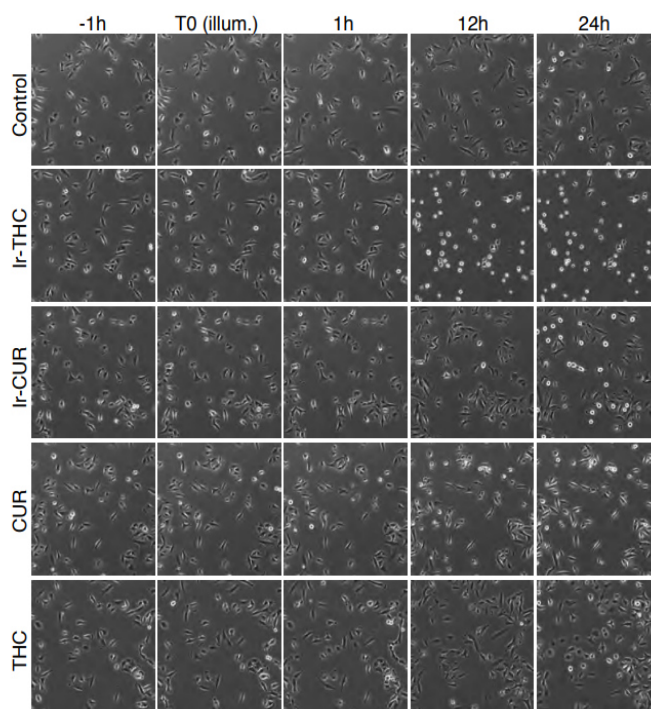


Figure 3 Sample images of the time-lapse experiment performed on A549 cells treated with Ir-THC for 2 h and the indicated compounds at $30 \mu\text{M}$ concentration before irradiation and recording. Cells were irradiated for 2 s in the wavelength range 465–495 nm (5.6 mW mm^{-2}) and this time point is considered T0.

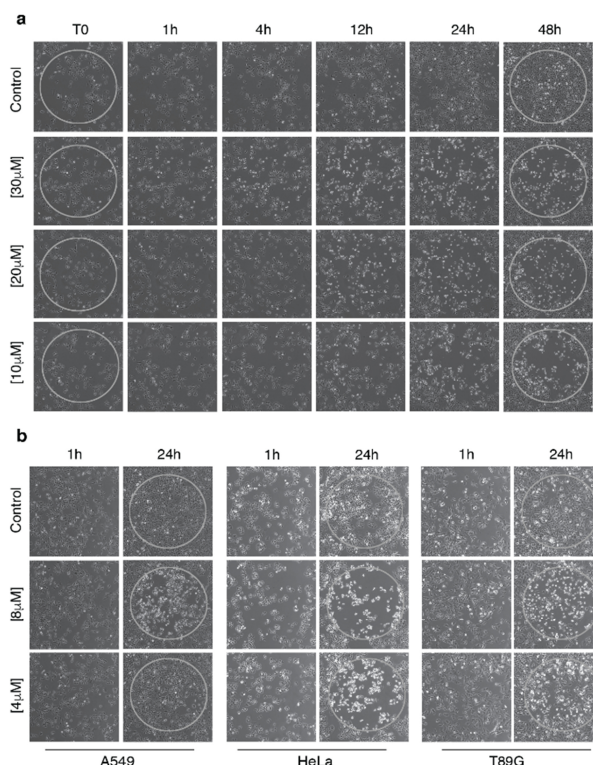
The Ir-CUR complex upon irradiation showed much reduced activity compared to Ir-THC, an observation that is consistent with the earlier conclusion of rapid deactivation of the excited state. It is remarkable to note that, for cells treated with the Ir complexes, neighbouring cells in the culture plates that were *not* subject to irradiation were perfectly viable. Free CUR

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showed limited phototoxicity whilst free THC did not show any such activity at all, demonstrating the fundamental role played by the coordination to the iridium(III) center for the phototoxicity. Subsequent experiments were conducted with Ir-THC at a range of lower concentrations. Results indicated that a dose of 10 μM is sufficient to kill all the treated cells when irradiated for 2 s (Fig. 4a). In order to assess the broader applicability to other cell lines, analogous phototoxicity experiments have been carried out on HeLa cells and human brain glioblastoma T89G cells, treated with 4 and 8 μM of Ir-THC. No evident differences are visible among the various cell lines, though A549 cells appear to be more resistant at 4 μM concentration (Fig. 4b).

Figure 4 (a) Sample images of the time-lapse experiment performed on A549 cells treated with Ir-THC at the concentrations indicated. Circles underline the



irradiated region of the wells. (b) Comparison of images obtained at 1 and 24 h treatment of A549, HeLa and T89G cells at 4 and 8 μM . Cells were irradiated for 2 s in the wavelength range 465–495 nm (5.6 mW mm^{-2}).

The LD_{50} (half lethal dose concentration) of the Ir-THC complex was calculated with the set parameters (2 h pre-incubation, 465–495 nm, 2 s irradiation) using the CCK assay in HeLa and A549. Ir-THC gave LD_{50} values of 5–7 μM . We also tested the effect of longer irradiation of cells treated with a lower concentration of complex. Strikingly, phototoxicity is visible even with 1 μM of Ir-THC, when cells are irradiated for 20 s (Fig S5, SI). These results are exceptionally promising for photodynamic therapy, since the phototoxicity index (PI) of the complexes is remarkably high (>200) and the time of light exposure is very low.

Conclusions

In conclusion, the new cyclometallated Ir(III) complex with a tetrahydrocurcumin ligand, Ir-THC, appears to be a very promising tool for combined photodynamic therapy and cellular imaging. It has several desirable properties for the purpose: (i) it is highly phosphorescent and soluble; (ii) it easily enters into cells where it is concentrated in mitochondria, even at limited concentration; (iii) it is highly phototoxic upon irradiation with suitable light, but not cytotoxic in the dark. These results highlight how photoactive metal complexes of curcuminoids may offer interesting future potential for phototherapeutic applications in combination with emission imaging microscopy.

Experimental Section

Experimental details are in the available Supporting Information: synthesis and NMR spectra, absorption and emission spectra of the Ir(III) complexes, cell lines, cellular uptake and staining, time lapse experiments, cell viability (MTT and CCK) assays.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: iridium complexes • curcumin

•tetrahydrocurcumin photodynamic therapy • anticancer agent

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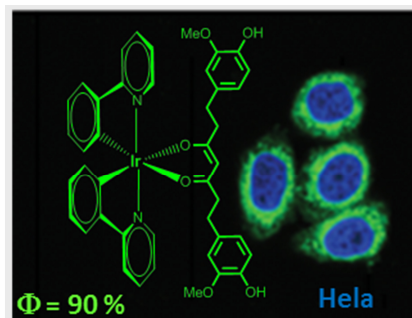
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Entry for the Table of Contents

Layout 1:

FULL PAPER

A novel highly phosphorescent cyclometallated curcuminoid Ir(III) complex, which easily enters into mitochondria, is highly phototoxic upon irradiation with suitable light, but not cytotoxic in the dark. It is an excellent tool for combined photodynamic therapy and cell imaging.



Alessia Colombo, Mattia Fontani, Claudia Dragonetti*, Dominique Roberto, J. A. Gareth Williams*, Rossella Scotto di Perrotolo, Francesca Casagrande, Sara Barozzi, Simona Polo* Page No. – Page No.

A highly luminescent tetrahydrocurcumin Ir(III) complex with remarkable photoactivated anticancer activity