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Triphenylamine Sensitized 8-Dimethylaminoquinoline: An Efficient Two-Photon Caging Group for Intracellular Delivery

Delphine Rigault,^[a] Philippe Nizard,^[a] Jonathan Daniel,^[b] Mireille Blanchard-Desce,^[b] Eric Deprez,^[c] Patrick Tauc,^[c] Hamid Dhimane,^[a] and Peter I. Dalko^{*[a]}

Dedicated to the memory of Dr. D. Ogden.

Triphenylamine-sensitized 8-dimethylaminoquinoline (TAQ) probes showed fair two-photon absorption and fragmentation cross sections in releasing kainate and GABA ligands. The water-

soluble PEG and TEG-analogs allowed cell internalization and efficient light-gated liberation of the rhodamine reporter under UV and two-photon (NIR) irradiation conditions.

Introduction

Light-sensitive probes^[1–5] and, in particular, photolabile protecting groups (“caged” substrates)^[6–17] which transiently inactivate the biological activity of drugs through specific covalent binding, continue to revolutionize biomedical sciences.^[18–26] They are powerful tools for studying cell signaling with appropriate spatio-temporal resolution and minimal unwanted interference. Although activation of most probes requires UV light, a handful of probes may undergo photolysis by using wavelengths in the near infra red (NIR). As NIR is less damaging to cells and penetrates deeper into tissues, these conditions are better suited to biomedical applications. Two-photon (2P) optimized caged probes^[27–32] have been widely developed and used in neurosciences,^[33–35] and are now gaining importance in other areas of cell biology and physiology. Despite the fact that several “caging” groups such as nitrobenzyl (NB), bromohydroxy coumarin (BhQ) and o-hydroxycinnamate (OHC) derivatives are known to have a certain degree of cell membrane permeability^[38,39] these compounds have mainly been used to study extracellular membrane receptors. In addition to low internalization efficiency, phototoxicity problems associated with the use of UV light for photoactivation as well as the small

2P uncaging cross-section have limited the value of these probes for intracellular studies.

Historically cell permitting intracellular probes were developed first to study the Ca²⁺ signalisation paths and was pioneered by Engels and Schlaeger who used cleavable ester groups by esterases to deliver pro-cAMP.^[40] Lipids with charged headgroups (i.e. phosphates, cholines, ethanolamines) have been delivered *via* microinjection and were shown detrimental to observing. Targeted photolysis proved to be a convenient alternative of activation, offering precise timing for the study of the underlying physiological process. Photolysis has been developed as a tool to release calcium chelators and donors in living cells, such as D-myo-inositol 1,4,5-trisphosphate (IP3)^[41] and cyclic ADP ribose.^[40] An intracellular photoactivation strategy has been developed for the liberation of cGMP from the freely soluble 7-diethylamino-courmarin (DEAC450) derivative upon irradiation at 453 nm. Also, an ingenious method was suggested for fluorescent labeling of recombinant proteins using the cell-penetrating octa-Arg peptide as a vector.^[42] Noteworthy, this latter method is much less disruptive to target proteins than other light-sensitive or enzyme-mediated labeling methods.

Most probes used for UV activation respond inefficiently to 2P activation. Optimization for two-photon activation of these probes remains a challenge, however, particularly in view of the many limitations that condition their use in physiological environments. The addition of extended and rigid π -electron systems with other judiciously placed electron donor/acceptor functionalities that generally increase the 2P absorption cross-section has invariably resulted in sparkling soluble probes in aqueous buffer. For this reason, only a few large chromophore systems have been proposed for cellular biology^[43–49] and only the Ca²⁺ BIST-EGTA complex has been developed for activation in intracellular spaces.^[50] While this ingenious system allows the delivery of amphipathic cargoes such as complexed Ca²⁺ to the cytosol, it is not compatible with the use of more general organic ligands. It has therefore long been considered that a “caging” group having large substrate scope that able deliver-

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ing the attached ligands in intracellular spaces with minimal perturbations to the cell would be particularly useful in cell biology for the dynamic study of signalling pathways.

Most intracellular drug delivery strategy aim enhancing endocytic uptake and releasing the therapeutic molecule from endocytic vesicles into the cytosol. However, the low rate of penetration through endocytic vesicle membranes and the degradation of macromolecules by lysosomal enzymes remain a major limitation.^[51,52] Another strategy to consider is the photochemical internalization (PCI) that is based on the endocytic activity of most-excepted mature erythrocytes-cell types followed by photochemical treatment of the internalized photosensitizer such as porphyrin or triphenylamine (TPA). The activated photosensitizer stimulates translocation of co-endocytosed macromolecules into the cytosol, according to the pioneering work by Berg et al.^[53,54] Cytosolic delivery requires thus the therapeutic macromolecules and photosensitizer to be located in endocytic vesicles at a certain stage of the process. PCI has been shown to enhance the biological activity of a variety of macromolecules that do not readily penetrate the plasma membrane. Based on the work of Berg et al.,^[53,54] we hypothesized that TPA attached to a PPG would trigger PCI. In addition, it has recently been shown that the addition of electron-donating TPA to a chromophore can induce intramolecular charge transfer (ICT) from donor to acceptor under photoexcitation in a D–A molecule, providing force-directed migration for electrons, leading to enhanced optical absorption capacity.^[55–57] Polarization can thus induce a major improvement in the uncaging quantum yield and 2P absorption,^[55] suggesting that this strategy could also be of interest for the 2-hydroxymethyl-8-(dimethylamino)quinolin (DMAQ) cages. Noteworthy, quinoline-derived probes are among the most sensitive probes used in neurosciences and cellular biology and have also been used for various light-gated ligation strategies, including iterative native chemical ligation (NCL) and expressed protein ligation (EPL)-desulfurization methods, enabling detailed study of protein structure-function relationships.^[28,58–65] It has been observed that the C(6) position of the DMAQ backbone presents a preferred entry point for molecular modification leading to enhanced photosensitivity,^[66] thus the general structure of the triphenylamine-sensitized DMAQ-derivative **1** was identified, as a lead (Figure 1).

In order to test our hypothese, substrates commonly used in neurophysiology, such as kainate and GABA were selected as ligands, attached *via* general ester and carbamate functions, thus testing the generality of the approach. The effect of PEG and triethylene glycol (TEG) *vs* free carboxylic acid solubilizing groups were also compared.

Results and Discussion

The synthesis of the key intermediate 6-iodo-8-DMAQ, **4**, is depicted in Scheme 1. The fluoro aniline starting material, **2**, was selectively iodinated and condensed with crotonaldehyde to furnish **3**. Quinaldine **3** was oxidized with selenium dioxide and the dimethylamino group was introduced by S_NAr sub-

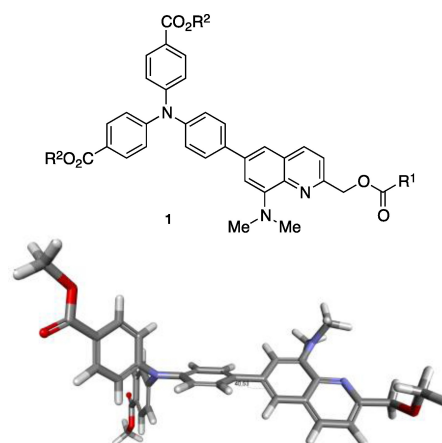
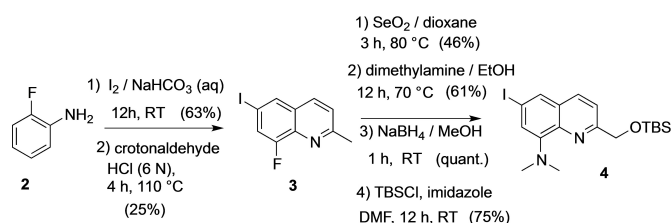


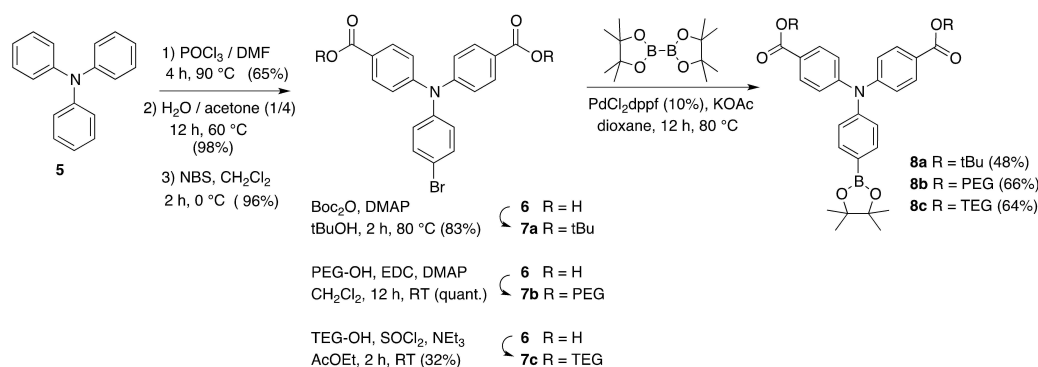
Figure 1. The general structure of the triphenylamine-sensitized 8-dimethylaminoquinoline (TAQ, **1**) and conformational analysis of the probe. For simplicity, ligand (R^1) and solubilizing groups (R^2) were replaced by CH_3 . Ligand conformation was generated using the Prepare Ligand module and the BEST algorithm^[67] within Biovia Discovery Studio 2022.



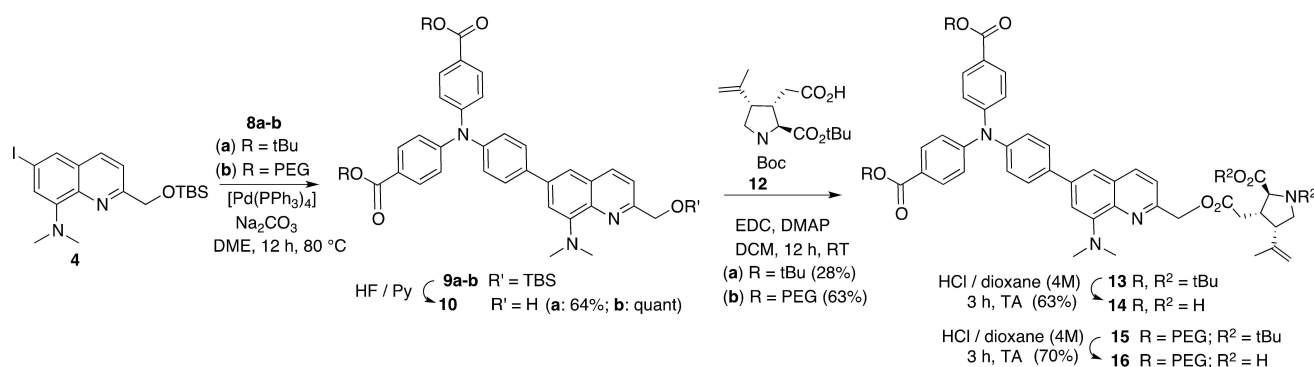
Scheme 1. Synthesis of the key intermediate **4**.

stitution and the aldehyde was reduced by $NaBH_4$ followed by protection of the free hydroxymethylene as TBS ether **4**.

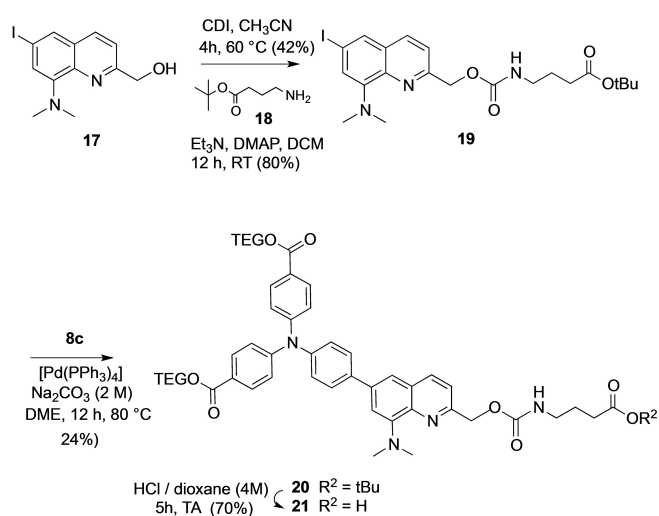
Functionalized TPA-antennas, **8a-c**, were prepared by selective formylation/oxidation esterification sequence (Scheme 2). The boronate group was installed by selective bromination followed by $PdCl_2dppf$ (10 mol%) mediated borination, using bis-pinacol boronate. The sequence was finalized by preparing thus the GABA and kainate derivatives, allowing also to compare different solubilizing groups, such as dicarbocyclic acids, di-PEG esters and di-TEG esters. For the preparation of the kainate esters, **14** and **16** the iodoquinoline intermediate **4** was coupled with triphenylamine boronates **8a-b** under Suzuki conditions (Scheme 3). The TBS-protected hydroxymethylene **9a-b** were converted to the corresponding kainate, and the *t*Bu protecting groups were removed to furnish the triamide **14** and the di-PEG derivative, **16**, respectively. The GABA-derivative **21** was prepared by condensation of the protected GABA to the imidazolyl urea activated intermediate, prepared from **4**. Suzuki-type coupling of the triphenylamine boronate antenna followed by deprotection of the *t*Bu protecting groups afforded the desired **21** (Scheme 4). Conformational analysis showed that in the most stable ground-state conformation, the TPA group and the quinolin chromophore are positioned at a dihedral angle of 40.5° , allowing partial electronic coupling between TPA and DMAQ groups (Figure 1).^[9] Functionalization of TPA with carboxyl linchpins



Scheme 2. Synthesis of the functionalized triphenylamine antenna.



Scheme 3. The assembly of the diacid and PEG-solubilized caged kainate.



Scheme 4. The assembly of the TEG-solubilized caged GABA.

enables the addition of solubilizing groups, or can be used for conjugation of targeting functions.

Probes were hydrolytically stable at pH 7.2 at 4 °C for 24 h (Figures 2a, and SI-3, SI-5). The UV spectra of **14**, **16** and **21** showed qualitatively and quantitatively similar patterns with the first absorption maxima $\lambda_{\text{abs}}^{\text{max}} = 351\text{--}354$ nm (SI and Table 1). Note that this value is very similar to that of the 8-DMAQ derivatives, indicating that the TPA and DMAQ units are

weakly coupled electronically and that there is no greater conjugation between these two parts. The large Stokes shift and the wide separation between excitation and emission wavelengths indicate efficient intramolecular energy transfer within the donor-acceptor electronic structure, with rapid relaxation from the initial to the emissive states.^[68] The presence of the TPA group resulted in high ϵ^{max} with values between 1.9 and 3.4×10^4 M⁻¹cm⁻¹ a value 1 log higher compared to the parent 8-DMAQ probe.^[61] The two-photon cross section $\delta_{2\text{PA}}$ was measured by the two-photon-induced fluorescence measurement technique (TPEF) using femtosecond (fs) laser pulses, and the TP absorption cross-sections (δ_a) of **14**, **16** and **21** were determined by the same manner as described before.^[60–62] Reasonable high 2P absorption cross sections for all compounds were observed, in the range of 30 to 45 GM (Table 1). All compounds undergo fragmentation upon irradiation at 365 nm (SI).^[62]

Uncaging quantum yield values (Φ_u) were determined in a 1/1 mixture of acetonitrile/TRIS buffer (pH 7.2) by using potassium ferrioxalate actinometry^[69,70] (SI) and the corresponding values are listed in Table 1. We note that the values depend strongly on the nature of the solubilizing substituents, as shown by the comparison of compounds **14** (22%) and **16** (13%). Similarly, compound **21**, which has a carbamate linker and GABA ligand (**21**), has a much lower value (Φ_u) than that of the kainic acid attached via an ester linker (**16**) (3%). The calculated 2P photosensitivity values δ_u ($\sigma_2^{\text{max}}\Phi_u$) (Table 1), show much

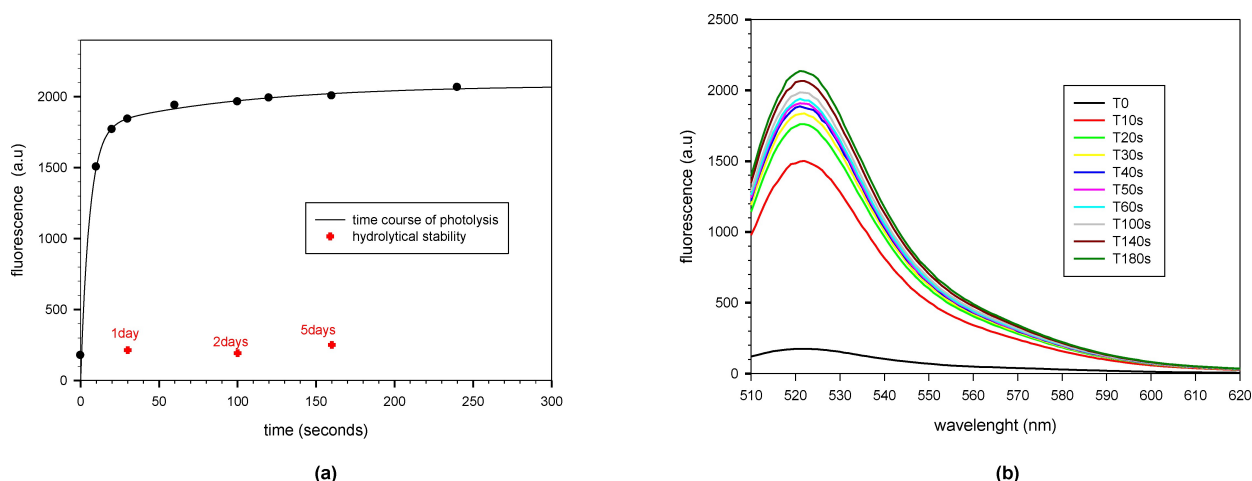


Figure 2. (a) Photolysis and hydrolytical stability of **24** in Tris (1 M aq.)/ACN 1/1 mixture in the dark at pH 7.2. Compound **24** was incubated for 5 days in the dark for control (red line) or irradiated with a 365 nm lamp for specified durations followed by measurements of the fluorescence intensity generated by photoreleased rhodamine ($\lambda_{\text{ex}} = 500 \text{ nm}$, $\lambda_{\text{em}} = 522 \text{ nm}$). (b) Time course of the photo-release of rhodamine followed by fluorescence of the liberated rhodamine.

Table 1. Mono and biphotonic photophysical characteristics of chromophores **14**, **16** and **21**.

Compound	$\lambda_{\text{abs}}^{\text{max}}$ [nm]	$\epsilon^{\text{max}} \times 10^4$ [$\text{M}^{-1} \text{cm}^{-1}$]	$\lambda_{\text{em}}^{\text{max}}$ [nm]	$\Phi_{\text{f}}^{\text{a}}$	$\lambda_{2\text{PA}}^{\text{max}}$ [nm]	σ_2^{max} [GM]	$\sigma_2^{\text{max}} \Phi_{\text{f}}$ [GM]	$\Phi_{\text{u}}^{\text{b}}$	$\delta_{\text{u}}^{\text{c}}$ [GM]
14	351	3.4	502	0.07	730	45	3.4	0.22	9.9
16	352	1.9	503	0.02	720	30	0.8	0.13	3.9
21	354	2.8	502	0.04	730	40	1.8	0.03	1.2

[a] Measured in acetonitrile/TRIS buffer (20 mM) 1/1 at 293 K. [b] Measured at 365 nm. [c] Samples were prepared in 0.1 mM concentration in acetonitrile/TRIS buffer 1/1 solvent mixture (pH 7.4). For full experimental protocol, see SI.

higher values than those of the corresponding parent DMAQ compound ($\delta_{\text{u}} = 0.67 \text{ GM}$).

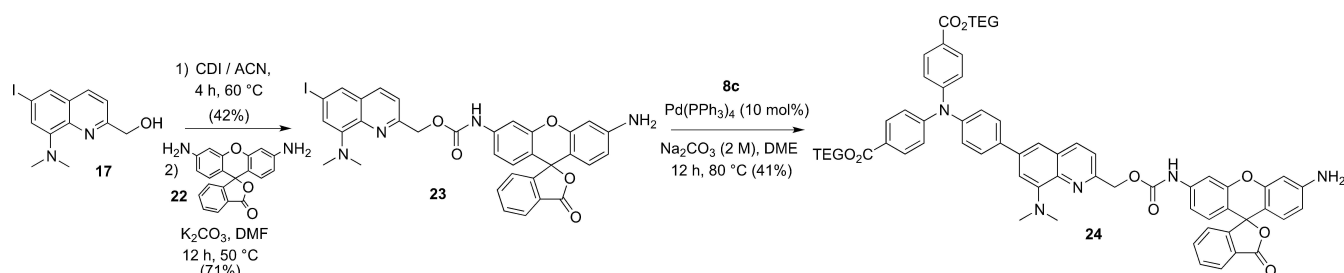
In order to demonstrate the potential of the probe rhodamine 110 reporter was caged (**24**) in two steps with 30% overall yield (Scheme 5). The sequence involved CDI mediated esterification and coupling of the TPA-boronate **8c**, and iodoquinoline **23** in the presence of $\text{Pd}(\text{PPh}_3)_4$ (10 mol%) under Suzuki conditions.

Compound **24** showed a slightly blue shifted maxima compared to the other derivatives ($\lambda_{\text{max}} = 348 \text{ nm}$, $\epsilon^{348} = 2.7 \cdot 10^4 \text{ M}^{-1} \text{cm}^{-1}$; $\epsilon^{365} = 2.3 \cdot 10^4 \text{ M}^{-1} \text{cm}^{-1}$, $\Phi_{\text{u}} = 0.24$) (See SI). Noteworthy, the fluorescence of the rhodamine was efficiently quenched in **24**, probably by resonance energy transfer (FRET) (Figure SI-8). The caged rhodamine probe **24** was hydrolytically

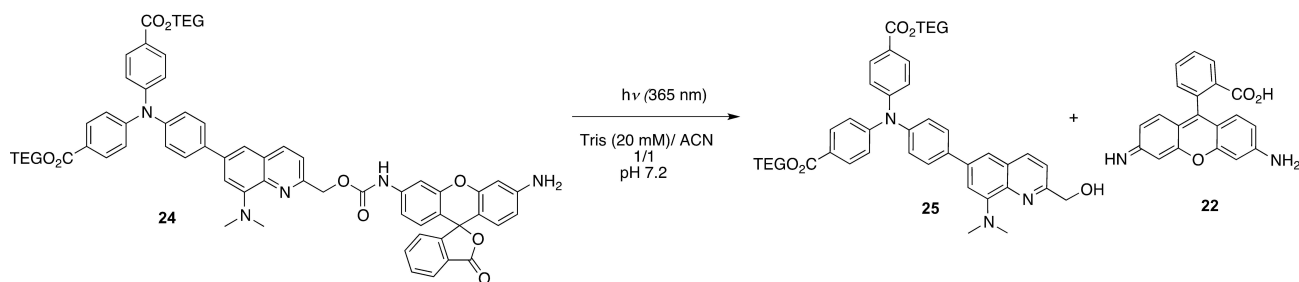
stable for at least 5 days since no fluorescence was detected when incubated in a Tris (0.1 M aq.)/acetonitrile 1/1 solvent mixture in the dark at pH 7.2 (Figure 2a).^[26]

The UV photofragmentation of **24** was studied in Tris (0.1 M aq.)/acetonitrile 1/1 buffer at 365 nm by using standard TLC lamp (Roth, 6 W) (Scheme 6 and Figure 2). The time course of the fragmentation was followed by monitoring the fluorescence of the liberated rhodamine **22** (Figure 2b). No further analysis of the released rhodamine was realized. The release time course showed a remarkably rapid appearance of rhodamine with $t_{90\%} = 75 \text{ s}$.

In order to evaluate the potential of the probe in intracellular studies, HeLa cells were incubated for 24 h with $2 \mu\text{M}$ and $20 \mu\text{M}$ of compound **24**, respectively, in medium (0.1% of



Scheme 5. Synthesis of the caged Rh110.



Scheme 6. Photolysis of the caged Rh110 by UV (365 nm).

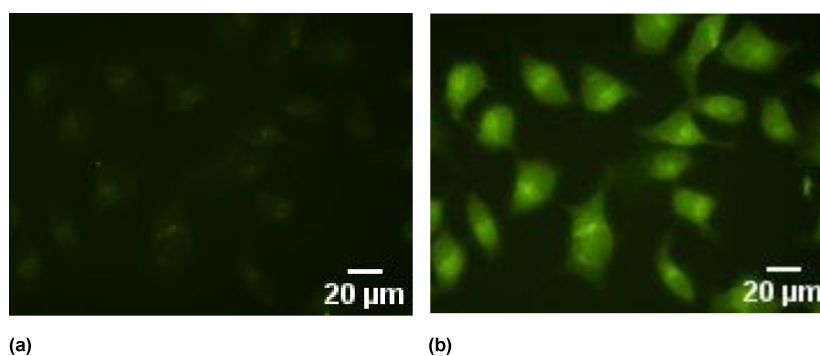


Figure 3. HeLa cells fluorescence pictures. HeLa cells were incubated with **24** (20 µM). (a) Cells before UV irradiation. (b) Picture of cells after activation by 357 ± 44 nm for 100 s. The fluorescence pictures were recorded with Nikon Eclipse TE-2000E widefield microscopy (20X) and processed with Image J. For the photolysis 350/50 excitation filter (DAPI) and a 525/36 (GFP) emission filter were used.

methanol final). As intracellular esterases are present in all cells, we first ascertained, that no fluorescence associated to free rhodamine in cells was present before UV activation (See SI). Rhodamine is known to diffuse from and into the cells, so the eventual free extracellular rhodamine was removed by refreshing medium before light activation.

The activation of the internalized probe, **24**, was realized with a standard DAPI light source at 357 ± 44 nm for 15 s and the fluorescence of the rhodamine reporter was collected by using GFP filter (EX 482 ± 25 /EM 524 ± 24) (Figure 3; for full experimental details see SI). Without irradiation the reference image is dark (Figure 3a), while (b) shows the efficient fluorescent staining of the cells showing efficient internalisation and uncaging of **24** with the DAPI light-source (Figure 4).

For 2P activation HeLa cells were pre-treated with a solution of **24** (20 µM) for 24 h and were exposed to 2P illumination using a pulsed laser source tuned at 760 nm. Fluorescence images, before or right after two-photon excitation, were recorded in the confocal mode with a SP2 confocal microscope (Leica MicroSystem), using a continuous laser line (488 nm) for excitation of the liberated rhodamine (emission slit: 490–590 nm). Images were evaluated qualitatively. The collected images show neat fluorescence origin from the intracellular liberation of the caged rhodamine in the regions exposed to light.

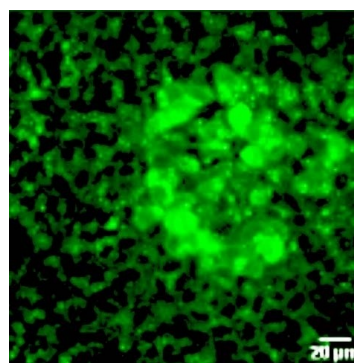


Figure 4. Fluorescence images of HeLa cells after 2P irradiation at 760 nm (1.25 W.cm^{-2}). 2P excitation was performed using a 80-MHz mode-locked Mai-Tai Ti:Sapphire tunable laser (720–920 nm, 100 fs pulse; Spectra Physics). Images were obtained in the confocal mode (EX 488 nm/EM 490–590 nm) by using a SP2 microscope (Leica MicroSystem) equipped with an oil immersion $\times 63$ objective (numerical aperture, 1.32) and an incubation chamber (37°C , CO_2 5%).

Conclusions

A small series of synthetic analogues and probes were prepared and evaluated for their absorption and emission properties under UV (365 nm) and 2P (730 nm fs pulsed) photolysis conditions, as well as for their water solubility, hydrolytic stability and ligand release. The synthetic objective of this study was rather to demonstrate easy access to several major caged ligands in the context of the new caging platform than to perform a systematic optimization that would also depend on

the objective of the final application. The 8-DMAQ-based triphenylamine-tethered water-soluble modular “caging” platform allowed for efficient internalization and *in cell* photo-activation of caged organic substrates both under UV (365 nm) and two-photon (760 nm) irradiation conditions. Probes **14**, **16**, **21** and **24** showed remarkably high photofragmentation efficiency under UV and 2P conditions (up to ~10 GM) *in vitro*, allowing the liberation of ester and carbamate linked kainate and GABA, respectively. Compounds were hydrolytically stable and showed no cytotoxicity when incubated with HeLa cells. The fluorescence of the rhodamine reporter was effectively quenched in **24** and showed internalization in HeLa cells after 24 h of incubation. The internalized probe was activated either by a DAPI light source (357 ± 44 nm) or, under two-photon activation conditions by a pulsed fs light source at 760 nm, and released the reporter in the light-exposed regions. This method could pave the way for the development of a general probe for intracellular studies enabling signaling pathways to be deciphered in a simple way.

Supporting Information Summary

The authors have cited additional references within the Supporting Information.^[59,69–74]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Light-sensitive probes · Two-photon activation · Caging group · Drug delivery · Intracellular delivery

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