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Synthesis and photocleavage of a new polymerizable [2+2] hetero dimer for phototriggered drug delivery

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ABSTRACT

7-Hydroxy-1,1-dimethylnaphtalenone is introduced as a versatile photocleavable linker system for drug attachment to polymer materials with significantly improved two-photon-absorption efficiency. The synthesis of TBDMS-protected 7-hydroxy-1,1-dimethylnaphtalenone monomer is described, which is the release group attached to the polymer moiety. The cytotoxic 5-fluoro-1-heptanoyluracil was photochemically attached via [2+2] cycloaddition to this release group. The linker–drug conjugate was photochemically polymerized into a HEMA/MMA copolymer. Photo-triggered drug release from the polymer via single-photon-absorption as well as two-photon-absorption in solution were carried out. The detachment of 5-FU from the polymer and its release from the polymer were monitored in the polymer as well as in the aqueous medium and multidose drug release was successfully demonstrated.

1. Introduction

Drug delivery systems are of interest in many medical applications. Sustained release is the most common method where the drug is released in a predetermined time profile beginning as soon as the system is applied to the patient. One example is the polymer microcapsules carrying water soluble drugs releasing them during decomposition of the capsules over several months [1]. But there is an increasing demand for controllable drug delivery systems, delivering well-defined doses of drug on demand. Implanted insulin pumps are a well-known example for this direction [2].

Our approach of controlled drug delivery is based on a photo cleavable linker system for drug release from polymer in cases where light access to the implant is possible. Such an example is intraocular lenses, where drug release needs to be accomplished from implanted IOLs years after cataract surgery for non-invasive treatment of posterior capsule opacification (PCO), so-called secondary cataract. After cataract surgery epithelial cells may proliferate on the polymer surface from the rim to the centre of the IOL and cause progressive deterioration of the visual acuity [3]. The incidence of PCO varies depending on the IOL materials and the age of patients, but are reported to lie in between 10% and 50% within 3–5 years after IOL implantation [4,5].

The phototriggered release is achieved by selective photocleavage of a cyclobutane moiety in the structure. Cleavage of the cyclobutane ring may be accomplished by single-photon-absorption (SPA) as well as by two-photon-absorption (TPA) triggered reactions. The TPA process may be illustrated as the simultaneous absorption of two photons each of half energy compared to one photon required for a SPA process. The TPA tool enables to control a photochemical reaction requiring light of ~260 nm, inside the eye. Such wavelengths are filtered off by the cornea. In addition, a precise 3D-spatial control of the photochemical reaction is possible. Early attempts to realize such a system were reported by Kim et al. [6,7]. Dicoumarins formed the photocleavable linker between a covalently attached drug and the polymer backbone, which causes that the drug is released with an undesired helper molecule attached [6]. Another approach was to bind the drug directly to the coumarin via [2+2]cycloaddition reaction [7,8]. However, coumarins and in particular dicoumarins have a very limited solubility in most solvents which makes synthesis rather difficult and additionally the lactone ring in coumarin-dimer is susceptible to hydrolysis [9,10] which leads to an undesired complexity in the photochemical cleavage reaction. The approach loading the lens polymer by mixing with derivatized oligomers [8] is restricted to low amounts of drug loading in the polymer. To overcome both types of problems a coumarin-analogue linker molecule, 7-hydroxy-1,1-dimethylnaphtalenone, which shows better sta-

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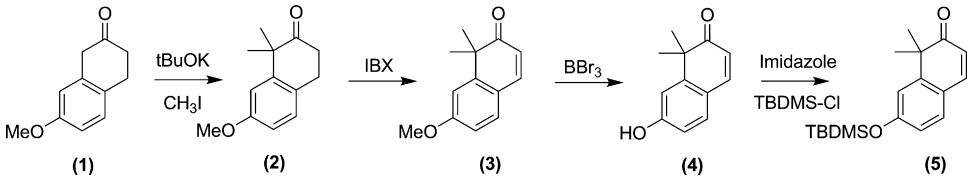

Fig. 1. Synthesis of 7-hydroxy-1,1-dimethylnaphtalenone.

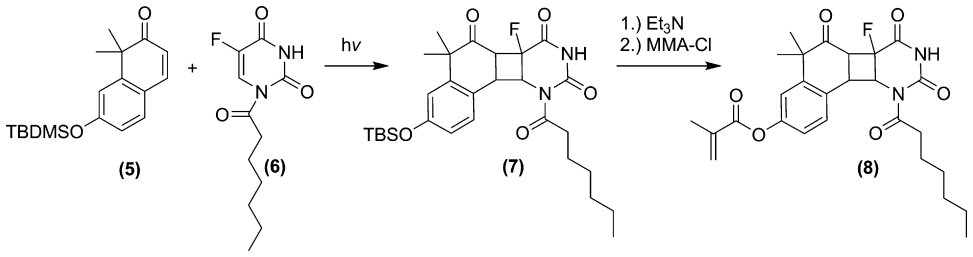

Fig. 2. Cross-dimerisation of 7-tert-butyldimethylsilyl-1,1-dimethylnaphtalenone **(5)** and 5-fluoro-1-heptanoyluracil **(6)** via [2+2] cycloaddition and attachment of the methyl-methacrylate monomer.

bility, better solubility and an improved two-photon-absorption coefficient [11] was synthesized and characterized for its application in such a drug delivery system.

Here we report the synthesis and characterisation of drug loaded polymer containing a new dimer composed of 1,1-dimethylnaphtalenone and 5-fluoro-1-heptanoyluracil. 5-fluoro-1-heptanoyluracil (H5-FU) proved to be a very suitable cytotoxic for treating posterior capsule opacification [6,12] and was bound directly to the 1,1-dimethylnaphtalenone monomer via [2+2] cycloaddition. This approach has the advantage that the drug is directly released and activated from the linker without any further remaining linker groups attached. We characterized the drug delivery from polymer material with respect to diffusion times and the ability of multidose applications. Upon detachment of the H5-FU from the polymer backbone and release from the polymer to the aqueous medium the heptanoyl residue is split off by amide hydrolysis [7] and the 5-FU remains.

2. Experimental

All chemicals were purchased from commercial suppliers and used without further purification. Organic solvents were received in technical quality and were purified by filtration and distillation before use.

2.1. Analytical

Standard NMR spectra were recorded on a Bruker Avance 300 B spectrometer (300 MHz) or on a Bruker DRX-400 NMR (400 MHz). Analytical RP-HPLC measurements were done on an UltiMate 3000 System (Dionex) equipped with a Nucleosil column (RP18, 5.0 μm, 250 mm × 4 mm, Bischoff Chromatography) using acetonitrile or methanol with ultra pure water (0.05 μS/cm), acidified with 300 μL H_3PO_4 per litre, as an eluent. For preparative RP-HPLC a YMC-Pack ODS-A column (C18, 5.0 μm, 250 mm × 4 mm, YMC) was used with an AD 25 absorbance detector and a P680 HPLC pump (both Dionex). LC/MS analyses were done on an ESI/MS LCQ Duo mass spectrometer (Thermoelectron) connected to a HPLC (1050-HPLC, Agilent Technologies) with a Nucleosil 100-3-C18 column (3 μm, 250 mm × 4 mm, Bischoff Chromatography). Heterodimers were prepared in an UV-reactor equipped with 12 fluorescent tubes Eversun 40 W/79, 25X (Osram). Photo-cleavage of heterodimers in acetonitrile was carried out at 266 nm in a fluorescence spectrophotometer type RF 1502 (Shimadzu). Photon densities at 266 nm were determined using a photodiode 1227-1010 BQ (Hamamatsu) with a correction factor of 1.1017 determined by actinometry with azobenzene for the fluorescence spectrophotometer at 266 nm. Two-photon-absorption experiments were done at 532 nm using a frequency-doubled Nd:YAG pulse-laser (Infinity 40-100, Coherent). All UV/vis spectra were recorded on a Lambda 35 (Perkin Elmer) in quartz cuvettes (Hellma).

Fig. 3. Round polymer blanks of 5-FU-loaded HEMA/MMA polymer.

2.2. Synthesis

2.2.1. Synthesis of 7-methoxy-1,1-dimethylnaphtalenone *(3)*

The synthesis of 7-methoxy-1,1-dimethyltetralone **(2)** was done, with some modifications, as described earlier[11]. 5.0 g (0.028 mol) 7-methoxy-2-tetralone **(1)** were dissolved in 40 mL of THF under argon atmosphere. The solution was cooled to 0 °C and 5.5 g (0.049 mol) potassium-*tert*-butoxide in 50 mL *tert*-butanol were added slowly. After stirring for 20 min methyliodide was added (3.6 mL, 0.028 mol) and the solution was stirred at room temperature for 2 h. The light sensitive product was purified via column chromatography on silica with 15:1 pentane: ethyl acetate yielding 4.4 g (79%) of white solid. For the introduction of the double bond (see Fig. 1) to 7-methoxy-1,1-dimethylnaphtalenone **(3)** iodoxybenzoic acid (IBX) was added as described earlier[11].

2.2.2. Replacement of the methoxy-protecting group by a tert-butyldimethylsilyl-group

The methoxy group was removed with boron tribromide (BBr_3). 1 g (4.96 mmol) of 7-methoxy-1,1-dimethylnaphtalenone **(3)** was dissolved in 160 mL dichlormethane under argon atmosphere and

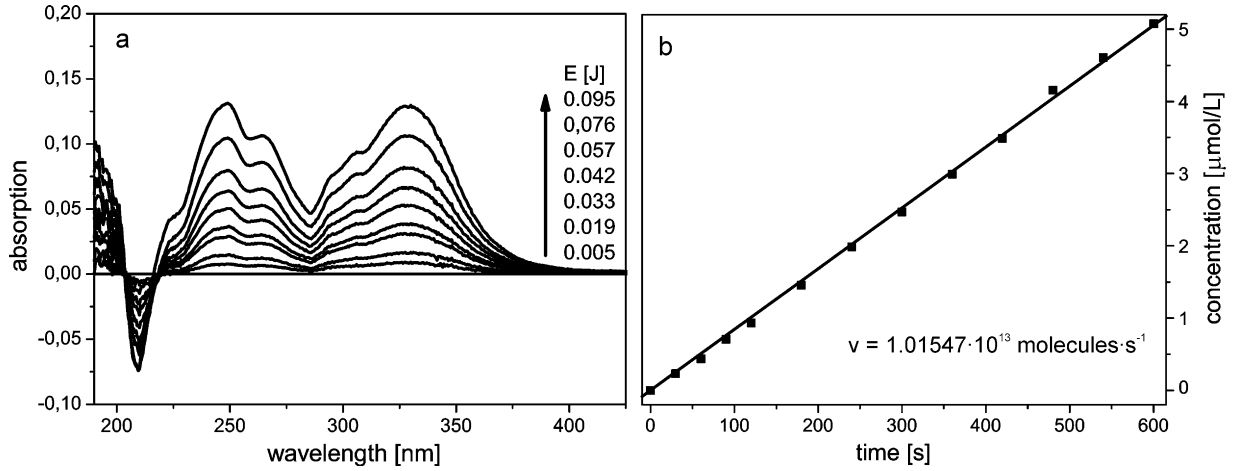

Fig. 4. Quantum efficiency of photochemical single-photon-absorption [2+2] cycloreversion of dimer. (a) UV/vis difference spectra monitoring the course of SPA cleavage. The rising absorption at 331 nm indicates the energy-dependent formation of the monomer **(3)**. (b) Time-dependence of **(3)** increase versus irradiation time. The number of cleaved molecules versus the number of absorbed photons was derived to be $\Phi_{SPA} = 0.010$.

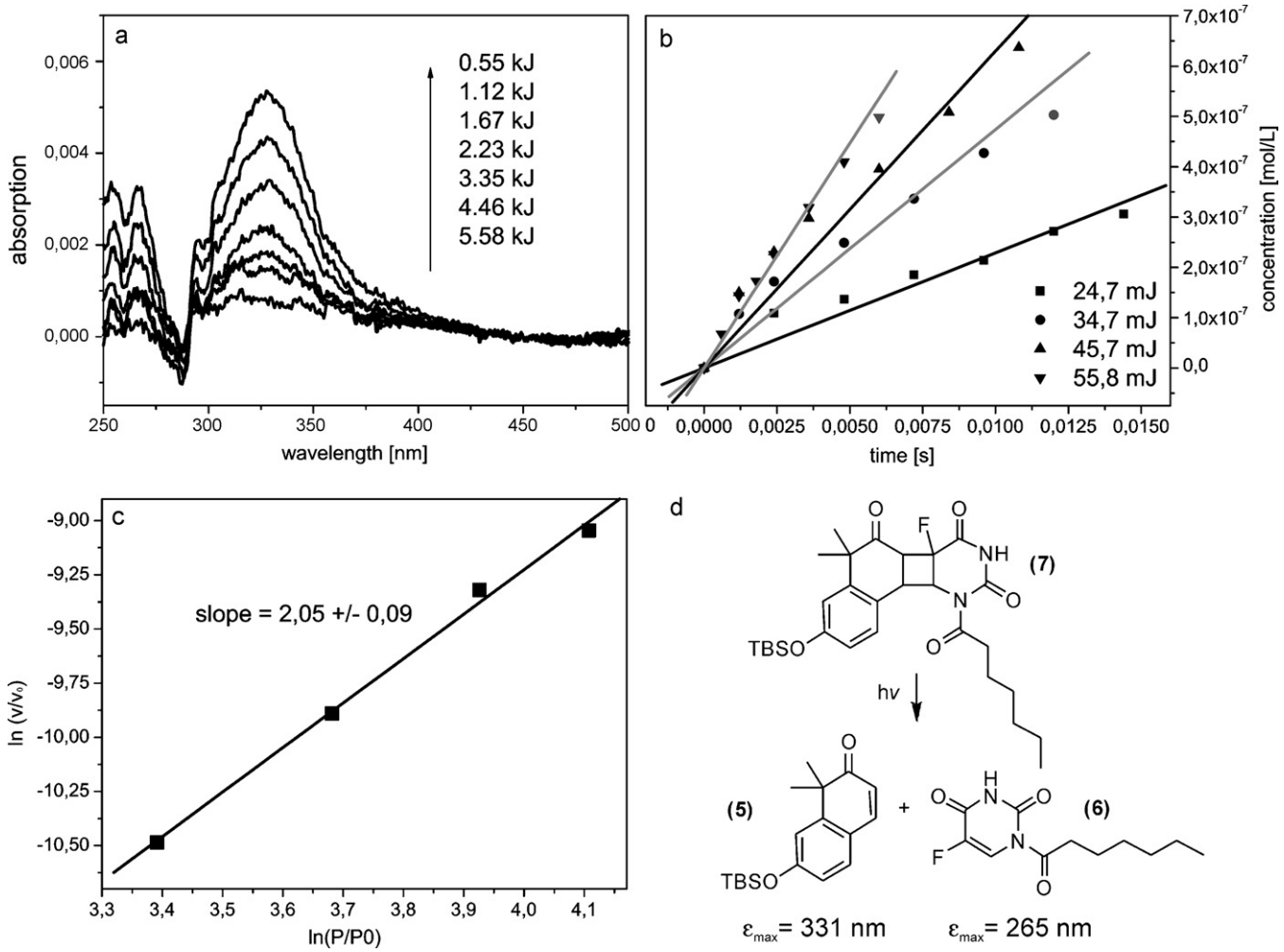

Fig. 5. Two-photon-absorption experiments of dimer **(7)** in solution. (a) UV/vis difference spectra monitoring the course of TPA cleavage. The rising absorption at 331 nm indicates the energy-dependent formation of the monomer **(3)**. The measurement for 55.8 mJ pulse energy is shown. (b) TPA induced cleavage at different energies. Monomer formation measured as the increase of the absorption at 331 nm in dependence on the incident laser power. (c) Double logarithmic plot of the applied laser intensities P versus the initial rates v_0 of the linker cleavage. The TPA induced nature of the photocleavage corresponds very well with the slope of 2 when ln v_0 is plotted versus ln P. (d) Photocleavage reaction from dimer **(7)** to the monomers and their respective absorption maxima.

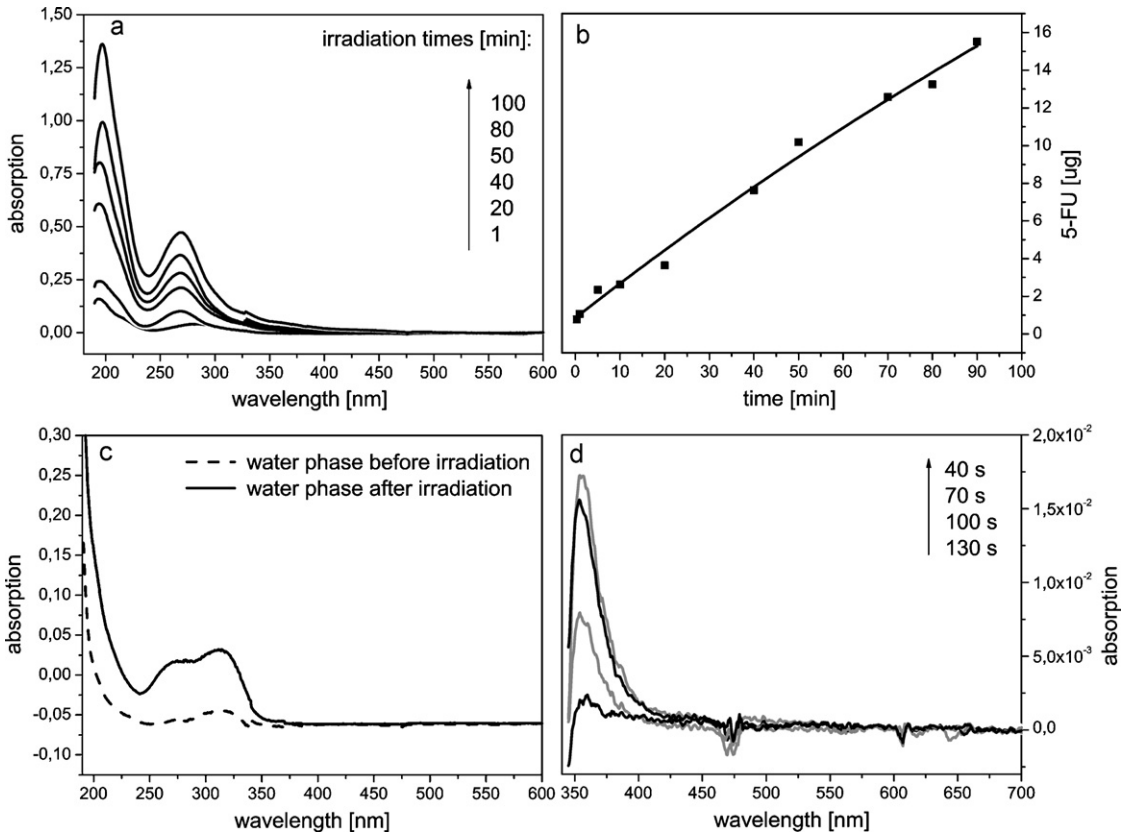

Fig. 6. Drug release experiments of the dimer in polymer. (a) UV/vis spectra of 5-FU at different irradiation times of the polymer showing the dependence of drug release on irradiation time. (b) Amount of 5-FU in [μg] of released drug calculated from the irradiation experiment shown in (a) and (c). Surrounding water phase of the lens before irradiation and afterwards. No release of 5-FU was detectable without exposure to the UV-C lamp. (d) UV/vis spectra of the lens itself after irradiation. The rising of the absorption at 331 nm of 1,1-dimethylnaphtalenon **(5)** is clearly shown and rises with releasing of 5-FU but remains still covalently attached to the polymer backbone. The polymer is completely non transparent for light below 350 nm, therefore only the raise of the absorption peak at 331 nm is detectable.

cooled to −78 °C. 5 equivalents (eq.) of boron tribromide (25 mL, 0.025 mol) were added and the solution was stirred for another two days. The reaction was quenched with 500 mL of water. Organic and water phase were separated and the water phase was extracted with dichlormethane. The solvent was removed and the obtained 7-hydroxy-1,1-dimethylnaphtalenone **(4)** was dried *in vacuo*. The yield was quantitative.

^{1}H NMR (300 MHz, CDCl3):

δ/ppm = 7.34 (d, 1H, J = 9.8 Hz), 7.17 (t, 1H, J = 6.8 Hz, J = 8.3 Hz), 6.93 (d, 1H, J = 2.3 Hz), 6.73 (dd, 1H, J = 2.4 Hz, J = 8.3 Hz), 6.0 (d, 1H, J = 9.8 Hz), 1.40 (s, 6 H)

^{13}C NMR (75 MHz, CDCl3):

δ/ppm = 158.4, 150.4, 145.7, 131.4, 121.7, 121.4, 113.9, 47.6, 28.1

M^+ calc 188.1, found 189.6

Tert-butyldimethylsilyl-chloride was chosen as a protecting agent for the hydroxy group. 7-hydroxy-1,1-dimethylnaphtalenone (1.0 g, 5.32 mmol) and imidazole (5 eq., 1.81 g, 0.027 mol) were dissolved in 120 mL tetrahydrofuran under argon atmosphere and 1.2 eq. of TBDMS-Cl (0.010 mol, 1.6 g) were added at room temperature and stirred for 8 h. The solvent was removed and the brown residue was dissolved in chloroform and washed with saturated $NaHCO_3$ solution and water. The chloroform

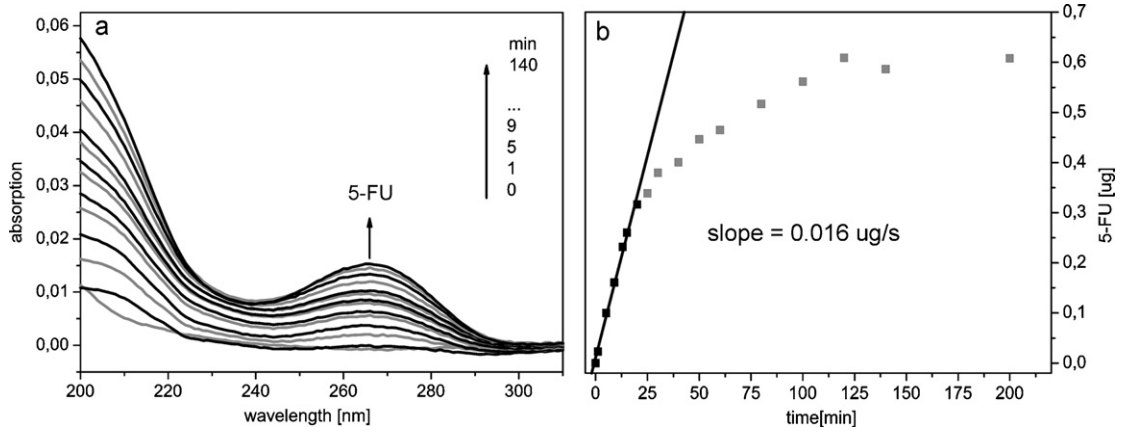

Fig. 7. Diffusion of 5FU out of the drug loaded polymer after irradiation. (a) UV/vis spectra recorded immediately after each irradiation step. (b) Calculated amount of released drug plotted versus irradiation times.

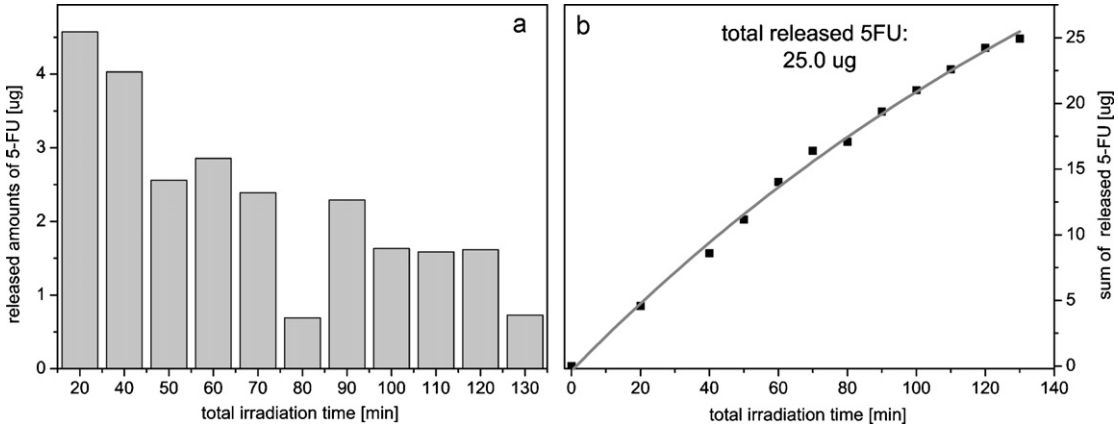

Fig. 8. Repeated drug release from polymer blank. (a) After irradiation the polymer was incubated in water for one week to ensure that released 5-FU diffuses completely out of the material. The released amount of drug was measured. (b) Total of cumulative drug release from the ten identical consecutive irradiations.

was removed and a brown oil was obtained. The oil was washed with methanol. An insoluble white solid was obtained and confirmed to be 7-*tert*-butyldimethylsilyl-1,1-dimethylnaphtalenone (1.3 g, 90%)

^{1}H NMR (300 MHz, CDCl3):

δ/ppm = 7.38 (d, 1H, J = 9.8 Hz), 7.29 (d, 1H, J = 8.3 Hz), 6.91 (d, 1H, J = 2.3 Hz), 6.74 (dd, 1H, J = 8.2 Hz, J = 2.4 Hz), 6.04 (d, 1H, J = 9.8 Hz), 1.44 (s, 6H), 0.99 (s, 9H), 0.23 (s, 6H)

^{13}C NMR (75 MHz, CDCl3)

δ/ppm = 203.5, 156.8, 148.9, 143.6, 129.9, 121.6, 121.1, 117.4, 117.2, 46.4, 27.0, 25.0, 24.7, 24.6, 17.3, 0.000, −4.0, −5.4, −6.2

M^+ calc. 302.5, found 304.2

2.2.3. Heterodimerisation of 7-tert-butyldimethylsilyl-1,1-dimethylnaphtalenone **(5)** and 5-fluoro-1-heptanoyluracil **(6)**

As 5-fluorouracile (5-FU) is more or less insoluble in relevant solvents for the dimerisation, a heptanoyl group was attached to one nitrogen to improve solubility. The heptanoyl group is quickly removed in aqueous solutions and therefore does not affect the cytotoxic activity [6]. H5-FU **(6)** was synthesized as described earlier [6] (Fig. 2).

The dimerisation of 7-tert-butyldimethylsilyl-1,1-dimethylnaphtalenone **(5)** and 5-fluoro-1-heptanoyluracil **(6)** was carried out in a Rayonett type photoreactor with wavelengths above 300 nm. The 7-tert-butyldimethylsily-1,1-dimethylnaphtalenone was dissolved in 10 mL of a saturated solution of 5-fluoro-1-heptanoyluracil with 10% of benzophenone in chloroform and degassed with argon for 15 min. Eight glass tubes were filled and sealed and the solutions were irradiated with UV light for 3–5 days. The reaction progress was monitored via HPLC. When the reaction was finished, the solvent was removed. The crude product was dissolved in acetonitrile/water (50:50) and stirred for 24 h at 40 °C in order to remove the heptanoyl group of excess 5-fluoro-1-heptanoyluracil. It should be noted that the heptanoyl group in the heterodimer is not affected under these conditions. The acetonitrile was removed by distillation, the 5-FU was filtered off and the watery phase was extracted with chloroform. The organic phase was dried, re-dissolved in acetonitrile and purified via isocratic preparative RP-HPLC with acetonitrile and acidified water (45:55) as an eluent. The heterodimer was obtained as a yellow solid (602 mg, 1.35 mmol, 23%).

^{1}H NMR (400 MHz, CDCl3):

δ/ppm = 8.35 (s, 1H), 7.27 (m, 1H), 6.84 (m, 2H), 5.40 (q, 1H, J = 8.7 Hz, J = 6.5 Hz), 4.23 (d, 1H, J = 8.6 Hz), 2.98 (m, 3H), 1.64 (s, 6H, 2 × CH_3), 1.30 (s, 8H), 1.0 (s, 9H), 0.87 (m, 3H, CH_3), 0.23 (s, 6H)

^{13}C NMR (75 MHz, CDCl3):

δ/ppm = 207.5, 173.7, 160.2, 148.8, 144.4, 132.3, 132.2, 117.3, 112.5, 112.2, 55.5, 55.18, 46.6, 41.4, 41.1, 38.9, 31.6, 29.5, 28.8, 24.5, 24.5, 22.6, 14.1, 1.1

^{19}F NMR (300 MHz, CDCl3): −155.6

M^+ calc. 544.7, found 543.7

2.2.4. Substitution of the TBDMS-protecting group for methyl-methacrylate

The 7-tert-butyldimethylsilyl-protecting group of the heterodimer **(7)** (40 mg) was removed with triethylamine (Et_3N, 8 eq., 83 μL) in dimethylformamide (1 mL) at 55 °C. The product was purified via isocratic preparative RP-HPLC with acetonitrile and acidified water (75:25) as eluent and yielded 29 mg (91%). It was identified via LC/MS (M^+ calc. 430.5, found 430.6).

For polymerisation methyl-methacrylate was covalently bound to the 7-hydroxy position. 160 mg dimer (0.31 mmol), 79.4 mg ethyl-(N′,N′-dimethylamino)propylcarbodiimide hydrochloride (EDC, 1.1 eq., 0.34 mmol) and 9.2 mg 4-(N,N-dimethylamino)pyridine (DMAP, 0.2 eq., 0.06 mmol) were dissolved in dichloromethane (25 mL) at 0 °C under argon atmosphere. 1.1 eq. (0.34 mmol, 28.3 μL) of methyl-methacrylate (MMA) were added and the mixture was stirred over night. The solution was extracted with 5% $NaHCO_3$ and brine. The organic phase was dried *in vacuo* and yielded 198 mg of a slightly yellow solid, the MMA-heterodimer **(8)** (95%). The product was analysed via NMR and LC/MS experiments. MS/MS experiments were carried out to verify the successful attachment of methyl-methacrylate at the naphtalenone-site in the heterodimer.

^{1}H NMR (300 MHz, CDCl3):

δ/ppm = 7.45 (m, 1H), 7.10 (m, 2H), 6.37 (s, 1H), 5.79 (s, 1H), 5.37 (q, 1H, J = 8.7 Hz, J = 6.8 Hz), 4.29 (d, 1H, J = 8.7 Hz), 3.06 (m, 3H), 2.08 (s, 3H), 1.67 (m, 6H), 1.33 (m, 10 H), 0.87 (m, 3H)

LC/MS: M^+ calc. 498.5, found 497.5

MS/MS on 497.5: M^+ of fragments = (4) + MMA: calc. 256.3 found 257.6; 5-FU calc. 129.1, found 127.9.

2.2.5. Photocontrolled co-polymerisation of drug–linker conjugate and HEMA/MMA

The polymer was prepared via photo-induced polymerisation at 470 nm. 43.3 g hydroxyethyl-methacylate (HEMA), 6.0 g methyl-methacrylate (MMA), 0.5 g ethylene-glycol-dimethacrylate (EGDMA), 0.1 g campherquinone and 0.1 g ethyl-4-dimethylaminobenzoate were mixed and degassed *in vacuo*. 90 mg of MMA-heterodimer were dissolved in 6 mL of the polymer mixture, degassed and filled into the polymerisation

cuvette (65 mm × 50 mm × 2 mm). The photo-polymerisation yielded a homogenous and optically clear plate, containing 1.5% weight percent of drug loaded heterodimer.

2.2.6. General polymer assays

The polymer was cut into round blanks of 6 mm diameter and 2 mm thickness, which were then analysed regarding 5-FU drug release.

For the tests the blanks were manufactured into lenses of 6 mm diameter and 1 mm thickness, weighting 20 mg each, which means an absolute amount of 75.9 μg 5-FU was contained in each lens. Every lens was incubated in water for six days for hydration at room temperature. In parallel testing was done at 37 °C. UV/vis measurements of the water phase in which the polymer lenses were incubated showed no release of drug.

3. Results and discussion

The photochemical properties of the heterodimer **(7)** as well as of polymer containing it in immobilized form were analysed regarding SPA and TPA induced cycloreversion in acetonitrile solution and its release from the polymer.

*3.1. Single photon and two photon absorption triggered drug release from heterodimer **(7)** and polymer*

For single photon absorption measurements a sample of heterodimer in acetonitrile was irradiated at 266 nm (c = 0.649 mmol/L). Cycloreversion of heterodimer **(7)** causes an absorption band with a maximum at λ = 331 nm from 7-hydroxy-1,1-dimethylnaphtalenon **(5)**, which results from the conjugated π-system between the carbonyl group and the double bond formed during cycloreversion of the cyclobutane ring. The heterodimer **(7)** and the released H5-FU/5-FU do not have any absorption in this region. This enables the use of the 331 nm band for monitoring and quantifying of the reaction.

Absorption spectra comprising the band at 331 nm of 1,1-dimethylnaphtalenone as a function of irradiation time are shown in Fig. 4a. The light energy of the lamp was measured to be 9.9331×10^{14} photons s^{-1}.

The efficiency of the SPA-induced photocleavage is characterized by the quantum yield Φ_{SPA} which is defined as the ratio of the number of molecules n_{Mol} cleaved by the number of photons n_{Phot} absorbed [11]. Because the absorption at 266 nm was beyond 2.5 it was approximated that all photons were absorbed

$$\Phi_{SPA} = \frac{n_{Mol}}{n_{Phot}}$$

The number of cleaved molecules was calculated from the initial reaction rate $v_0\,(t \to 0)$ according to Lambert–Beer's law. The cleavage of 1,1-dimethylnaphtalenone causes an absorption band with a maximum at λ = 331 nm. The extinction coefficient is ε_{331} = 10,250 L × mol^{-1} cm^{-1} [11]. Neither the H5FU nor the heterodimer show any absorption in this region. The initial reaction rate was determined to be $v_0 = 1.01547 \times 10^{13}$ molecules s^{-1} as shown in Fig. 3b. The quantum yield Φ_{SPA} was calculated to be Φ_{SPA} = 0.010 = 1% (Fig. 4).

Irradiation of the dimer **(7)** in acetonitrile (c = 1.964 mmol/L) with intense 532 nm pulses (20 Hz, 3 ns) causes TPA-induced cleavage of the heterodimer (Fig. 5). The formation of **(5)** is monitored at λ = 331 nm. An increase in the absorption indicates the cleavage of the cyclobutane-linker.

The change in absorption should be linearly proportional to the applied irradiation energy. In order to verify this, the TPA cross section was measured at four different energies (24.7 mJ, 34.7 mJ, 45.7 mJ and 55.8 mJ) (Fig. 5b). The change in concentrations of **(5)** was plotted against the irradiation time for the different pulse energies to obtain the initial reaction rates v_0. In most cases reported in the literature the quantum yield of the TPA has been assumed to be the same as for SPA [13–15]. Assuming this the TPA absorption cross section was calculated to be 1.81 GM which is almost twice as high as for dicoumarin [6]. In a double logarithmic plot of the initial reaction rate versus the intensities P a linear slope of 2.05 results [16,17] which confirms the two-photon nature of the process.

3.2. Characterisation of the drug loaded polymer material

A lens was irradiated with an UV-C lamp (Philipps TUV, PL-S, 9 W). The lens as well as the water phase surrounding the lens was analysed via UV/vis.

Without any irradiation, no drug was detectable even after several days. Only after irradiation with high intensity light a release was detected (Fig. 6a) and the amount of 5-FU released was found to be dependent on irradiation times (Fig. 6b). In the lens material a rise of the absorption band of remaining naphtalenone group, which is still covalently bound to the polymer moiety, was observed (Fig. 6c) whereas in the water phase the characteristic absorption at 265 nm of 5-FU was detected (Fig. 6d). After the experiments the water phase was concentrated and additionally analysed via HPLC, where solely 5-FU was identified as product from the photo triggered [2+2] cycloreversion.

3.3. Diffusion of drug out of the polymer material

The diffusion of released 5-FU from the polymer was measured by irradiating a lens for a few seconds and monitoring the absorption band of 5-FU at 265 nm via UV/vis directly afterwards (Fig. 7).

The release rate form the polymeric lens was determined to be 0.016 μg/s and the total drug release after 24 h incubation in water was 9.0 μg. For cataract treatment we calculated a minimum amount of 1 μg for a sufficient cytotoxic activity. After 20 min one third, i.e. 3.1 μg were already released from the polymer material which is a promising result for secondary cataract treatment giving a quick and high initial drug dose. The water phase was concentrated and analysed via HPLC showing only 5-FU as a product again.

3.4. Multiple drug releases from drug-loaded polymer

Another requirement of the system was the possibility of a multidose drug release. A piece of polymer of 2 mm thickness, weighting 21.6 mg, was irradiated ten times for 10 or 20 min. After each irradiation step the polymer piece was incubated in water for one week and the released amount of 5-FU was measured via UV/vis before the next irradiation step (Fig. 8).

With each irradiation step smaller amounts of 5-FU were released, but in each irradiation more than 1.0 μg were released and proving the multidose capability of these polymers.

4. Summary and conclusions

The synthesis and dimerisation of monomers and drug loading of HEMA/MMA photopolymer with 5-FU was successfully carried out. The 7-hydroxy-1,1-dimethylnaphtalenone revealed to be a suitable linker for reversible covalent attachment of the cytotoxin 5-FU to the polymer backbone. The 5-FU is reversible attached to the linker via [2+2] cyclo-addition and -reversion. Single-photon-absorption as well as two-photon-absorption cycloreversions of the dimer were successfully carried out, the released doses are more than adequate for cataract treatment and repeating the drug release with sufficient drug doses is possible. The SPA of the novel linker system was found to be Φ_{SPA} = 0.010. The TPA

cross section in solution was determined to be 1.81 GM, which is lower than the TPA for the naphtalenone homodimer but higher than for the coumarin dimers. This continuative processing of photocontrolled building blocks into polymer matrices takes another step towards its final application for TPA triggered drug delivery.

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