Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202302295
Chemistry Europe
European Chemical Societies Publishing
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Hot Paper

# Molecular Syringe for Cargo Photorelease: Red-Light-Triggered Supramolecular Hydrogel

Anna-Lena Leistner,[a] Mario M. Most,[a] and Zbigniew L. Pianowski*[a, b]

Photochromic supramolecular hydrogels are versatile materials that show macroscopic effects upon irradiation, like liquefaction or shape changes. Here, we demonstrate a simple photochromic cyclic dipeptide (2,5-diketopiperazine-based) supergelator, composed of (*S*)-lysine and an azobenzene analogue of phenylalanine, that forms supramolecular hydrogels even at 0.1 wt% loading. The gels can physically encapsulate cargo molecules and release them to the environment in a controllable manner upon irradiation with red light, thus working as a "molecular syringe". As the material is biocompatible and operational in the "therapeutic window" of light (>650 nm) that deeply penetrates soft human tissues, it is applicable to smart drug-delivery systems.

Phototriggered smart materials[1] hold increased promise for the delivery of therapeutic compounds[2] or solar-thermal energy storage.[3] For applications in a biological context, it is optimal to work with visible-light-responsive systems.[4] The most suitable range (650-900 nm) is called the "therapeutic window", as negligible absorption of these frequencies by hemoglobin and tissues enables deep penetration of soft human tissues.[5]

An increasing collection of molecular photoswitches operating in that range of excitation frequencies comprises tetra-*ortho*-substituted azobenzenes bearing alkoxy groups or halogen atoms,[6] as well as heterodiazocines,[7] dihydropyrenes,[8] indigoids,[9] arylhydrazones,[10] or imidazole-based systems.[11]

Here, we decided to combine the tetra-*ortho*-chloroazobenzene photoswitch with a simple hydrogelator motif[12] based on cyclic dipeptides (CDPs).[13] Previously,[14] we demonstrated efficient and reversible photodissipation of similar azobenzene-decorated CDPs with UV or green light, and their applicability for encapsulation and light-controlled release of drugs and biopolymers. Now, we developed a red-light-triggered "molecular syringe" based on the CDP **1**, which ejects previously encapsulated cargo in response to red light (Figure 1).

To synthesize the tetra-*ortho*-chloro azobenzene chromophore in **1** we applied the late-stage chlorination strategy,[15] which – along the addition of organolithium reagents to diazonium salts[16] – is among the most efficient synthetic strategies for these sterically hindered azobenzenes. Briefly, (*S*)-phenylalanine (Phe-OH) was nitrated in the *para* position, N-acetylated, and the nitro group subsequently reduced to amine with $H_2$ on Pd/C. The product **4** was subjected to Mills reaction with nitrosobenzene, yielding the azobenzene amino acid **5** in multigram scale (Scheme S1 in the Supporting Information). The subsequent key step – tetra-*ortho* chlorination of **5** (Scheme 1) – was performed in a sealed tube, 20 °C above the boiling point of acetic acid, with excess of NCS resulting in **6** (54 % yield) on a gram scale. Our previous attempts to use the unprotected version of **5** or its *N*-Boc analogue as substrates were unsuccessful. Next, the acetyl group was removed from **6** under acidic conditions (reflux in 6 M aq. HCl for 24 h). The precipitated product **7** was unfortunately fully racemized, as confirmed by chiral RP HPLC (Figure S22). The racemic **7** was

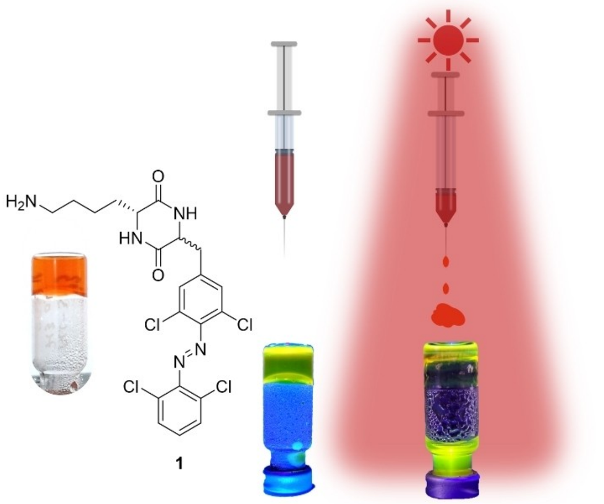


**Figure 1.** The hydrogel (orange) formed from **1** (here 0.3 wt%) in aqueous buffer can physically encapsulate cargo substances (yellow) and act as a molecular syringe. Upon irradiation with biocompatible red light (660 nm), the buffer with cargo is ejected from the gel, while in darkness the composition remains stable.

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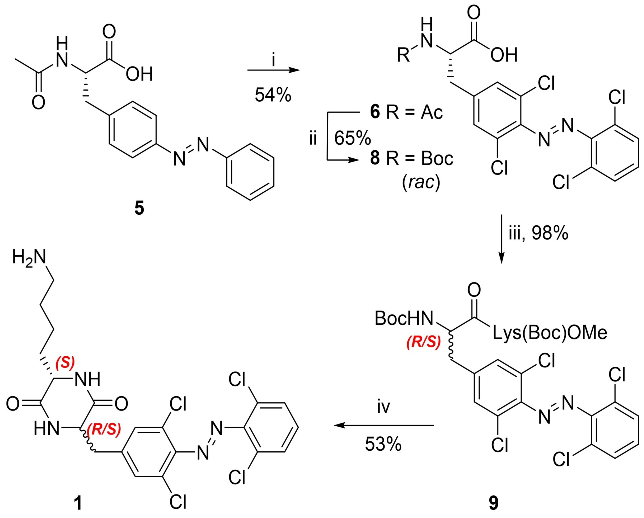
Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202302295




**Scheme 1.** Synthesis of the gelator **1**. i) NCS, $Pd(OAc)_2$, AcOH, 140 °C, 2.5 h; ii) 6 M HCl, 110 °C, 24 h; then $Boc_2O$, $NaHCO_3$, dioxane/water, 20 °C, 20 h; iii) HBTU, DIPEA, H–Lys(Boc)–OMe HCl, DMF, 20 °C, 2 h; iv) TFA, DCM, 20 °C, 1 h, then AcOH, 4-methylmorpholine, DIPEA, butan-2-ol, 120 °C, 2 h.

Boc-protected to **8**, then coupled with a commercial Boc-protected *(S)*-lysine derivative H-Lys(Boc)–OMe·HCl, yielding a mixture of diastereomeric dipeptides **9 a** and **9 b**. Then, the Boc protecting groups were removed quantitatively, resulting in crude **10**, which was directly subjected to the final cyclization that ultimately yielded the diastereomeric mixture (denoted "**1**") of CDPs (Scheme 1). The final diastereomeric ratio of 7:3 in precipitate isolated after the reaction (Figure S23) indicates different cyclization rate or solubility of the diastereomers in the reaction medium. Part of the mixture **1** has been separated by preparative RP-HPLC onto the more polar major product **1 a**, and the less polar diastereomer **1 b** (minor component), which were characterized separately. Most meaningful differences were the chemical shift of the hydrogen atom located at the stereocenter in the $^1$H NMR spectroscopy – **1 a** (3.81 ppm) and **1 b** (3.65 ppm; Figure S30), as well as the C=O stretching vibration of the conjugated ketones in the DKP ring in the IR spectroscopy (Figure S31).

Unequivocal assignment of **1 a** and **1 b** to the respective configuration was not possible so far. The overall low solubility in volatile solvents hampered the approaches to grow crystals. And slow evaporation of solutions in mixtures of water and acetonitrile resulted in amorphous material, which overall prevented X-ray structure determination.

Photochromism of **1 a** and **1 b** (Figures S1 and S2) was similar to other known tetra-*ortho*-chloroazobenzene derivatives.[6d,16–17] Even though the molar extinction coefficient $\varepsilon_{660\ nm}$ is below 10 $M^{-1}cm^{-1}$, red light (660 nm) irradiation resulted in the strongest shift of the molar absorptivity (Figures S3 and S4). The ratio of photoisomers at the respective photostationary states (PSS) were determined by HPLC. Red light irradiation (660 nm) yielded 85 % (*Z*)-**1**, violet light – 12 % (*Z*)-**1**, and green light (523 nm) – 53-55 % of (*Z*)-**1** (Table S2). The thermal half-life at 60 °C in AcOH is 4.39 h for (*Z*)-**1 a** and 5.07 h for (*Z*)-**1 b** (Figures S5–S7) – lower than for simple tetra-*ortho*-fluoro derivatives,[18] but higher than the fluorinated azobenzenes with extended π-electron system triggered with red light.[6b]

We also investigated biological stability of our gelator **1** (0.1 mM) using standard conditions that mimic intracellular reducing potential with 10 mM reduced glutathione and 5 mM TCEP in PBS buffer pH 7.4 with 5 % (*v*/*v*) DMSO at 25 or 37 °C. We did not observe any significant degradation over 24 h (Figure S8).

Next, the crude "**1**" (diastereomeric mixture of **1 a**/**1 b** 7:3, produced in the cyclization reaction) was suspended in PBS buffer (phosphate-buffered saline, pH 7.4; Table S3) and boiled for a short period of time, which resulted in homogenous hydrogels at the decreasing concentrations from 2.0 wt% until 0.1 wt%, stable upon vial inversion (Figure 2a). 0.1 wt% is more than ten times lower than the critical gelation concentration of the fluorinated analogue.[19] Further decrease of concentration to 0.05 wt% resulted in mechanically unstable viscous material. Hydrogels prepared in Ringer's solution (0.1–0.3 wt%) were generally less stable (Table S4) and therefore disregarded in further investigation. Hydrogels prepared in PBS buffer at the concentration of 0.3 wt% of **1** or higher were stable in a boiling water bath, while at lower concentration upon increasing temperature the gel shrank and released slightly colored liquid (Figure 2b). This process was reversible by heating the samples over the boiling point in a closed vessel.

Recombination of the HPLC-purified diastereomers to the originally isolated ratio of 7:3 (**1 a**:**1 b**) resulted in stable gel formation at the concentration of 0.1 wt% and higher, with similar shrinking behavior observed upon heating. Equimolar mixture of **1 a** and **1 b** (1:1) formed stable gels at 0.2 wt%.

Pure **1 a** formed gels at 0.2 wt% and shrinking was observed starting from 90 °C. To obtain a material with comparable behavior, 0.3 wt% of pure **1 b** were necessary (Table S5, all samples in PBS buffer). Thus, we conclude that both individual diastereomers **1 a** and **1 b** are efficient super-hydrogelators, but their combination at the 7:3 ratio ("**1**") shows at least similar, if

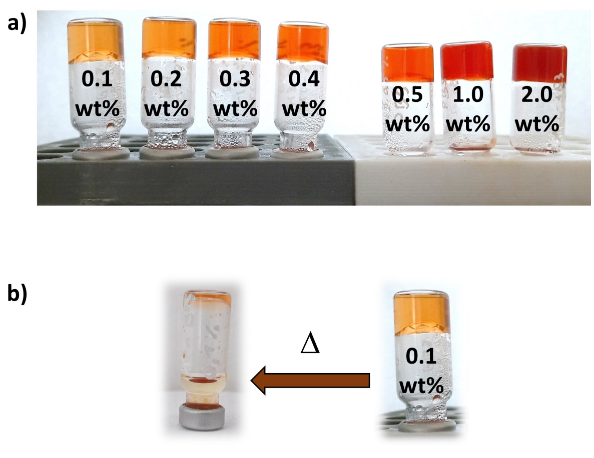



**Figure 2.** Supramolecular hydrogels made of **1** in phosphate-buffered saline (PBS) pH 7.4. a) Overview of the mechanical stability for samples in the concentration range 0.1–2 wt%. b) Heat-induced (> 74 °C) gel shrinking (0.1 wt% **1** in PBS) with concomitant liquid ejection.

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not slightly superior gelating behavior, and therefore isomer separation is not critical for further experiments.

Irradiation of all the aforementioned gel samples with red light resulted in shrinking (Figure 3 sample **b**) similar to the reaction upon exposure to heat (Figure 2b). Further irradiation with blue light (455 nm) restored the majority of (*E*)-**1**, but it did not reconstitute the original gel (Figure 3 sample **c**, the ejected liquid remained unabsorbed). The closed vial was then warmed up until boiling for short time and cooled down again. This yielded again a stable gel that absorbed all previously expelled liquid, with all parameters comparable to the original non-irradiated sample.

In comparison with relatively flat fluorinated or unsubstituted (*E*)-azobenzene chromophores,[14a,b,19] the sterically hindered *ortho*-chlorinated (*E*)-azobenzene shows a twisted structure that can assume three conformations in crystals.[6a]

To exclude the photothermal effect, another gel sample (0.1 wt%) was wrapped in aluminium foil and irradiated for 90 min with 660 nm under the same conditions. There, we observed no ejection of the liquid. We postulate that the photoinduced shrinking effect and ejection of the aqueous buffer is caused by conformational changes resulting from *E*→*Z* photoisomerization with red light. Yet, the *E* isomer restored with blue light might assume another sterically less favorable conformation within the hydrogel network – in comparison with the *E* isomer obtained upon thermal equilibration. Therefore, only boiling in a closed vessel restores the original gel constitution.

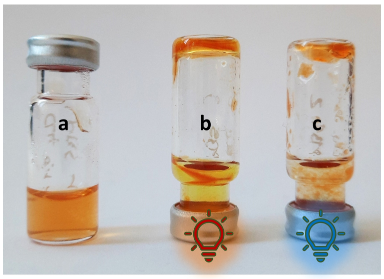


**Figure 3.** Hydrogel "**a**" formed from an equivalent mixture of diastereomers **1 a** and **1 b** (total conc. 0.1 wt%) was irradiated with red light (660 nm, 90 min) (sample "**b**") causing gel shrinking with liquid ejection that was, however, not reversible upon irradiation with blue light (455 nm; sample "**c**"), even though the majority of the *E* isomer of **1** was restored under these conditions.

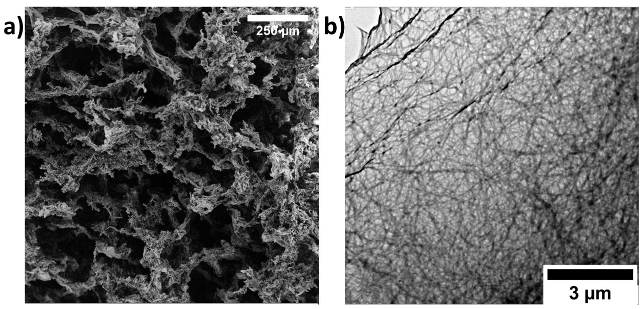


**Figure 4.** Electron microscopy imaging of the hydrogel samples prepared from **1** in PBS buffer at pH 7.4. a) SEM image of a xerogel composed of 1.0 wt% of **1**; scale bar: 250 µm. b) TEM image of a hydrogel composed of 0.1 wt% of **1**; scale bar: 3 µm.

Mechanical stability of the hydrogels formed from **1** (**1 a** and **1 b** at the 7:3 ratio) was assessed by rheological measurements at the concentrations of 1.0 and 0.3 wt% of the gelator in PBS buffer pH 7.4. The values of $G'$ and $G''$ were, respectively, $6\times10^3$ and $7\times10^2$ Pa for 1.0 wt% ($\tan\delta = G''/G' = 0.10$ at 1.14 Hz; Figure S12) or $1.3\times10^3$ and $2.5\times10^2$ Pa for 0.3 wt% ($\tan\delta = G''/G' = 0.14$ at 1.14 Hz; Figure S11). Thermal stability was also conferred (Figure S13). The results indicate, that the compound **1** forms proper hydrogels with mechanical stability comparable (yet, at the significantly lower critical gelation concentration) to other supramolecular hydrogels developed by our group.[14,19]

Scanning electron microscopy (SEM) revealed porous networks (Figure 4a) with density decreasing proportionally to the initial gelator concentration (Figures S14–S16). At the lowest concentration achieved for stable hydrogel, the observed porous structures were only rudimentary (Figure S14). We observed similar structures previously.[20]

Transmission electron microscopy (TEM) images show fibrous networks comparable to other hydrogelators investigated in our group (Figure 4b, Figure S19).[14a,b,19] Significant morphology changes have been perceived upon exposure of the samples on heat or on 660 nm irradiation, however the fiber network is conserved (Figures S17 and S18). It corroborates with lack of the complete light- or heat-induced gel dissipation to fluid – the process that was previously observed for non-halogenated and *ortho*-fluorinated LMWGs of similar design.[14,19]

Drug delivery is the desired application for stimuli-responsive soft materials. So far, upon irradiation of photochromic hydrogels produced in our group,[14,19] the complete liquefaction of the material occurred with concomitant cargo release. Here we demonstrate release of cargo previously encapsulated in a hydrogel made of **1** upon its light-induced shrinking. The cargo – a fluorescent dye 5(6)-carboxyfluorescein **2** – has been added (50 µg of **2** per vial) to a hydrogel formed from 0.2 wt% of **1**. To induce the release of **2**, vials were mounted upside down in an irradiation chamber and irradiated at 660 nm until the gel visibly reduced to 25–50% of its former size and fluorescent liquid was released (Figure S10a). The liquid accumulated at the bottom of the vial, while the shrunken gel remained attached to its top surface (Figure 5). We quantified (Figure S9 and Table S6) the amount of **2** released to the non-viscous liquid at the bottom of vials – after 2.5 h, we obtained 17 µg (30%) of **2**, and after 4 h: between 29 (59%) and 35 µg (66%) of **2** in two independent experiments. To exclude the photothermal effect, another gel sample was wrapped in aluminum foil and irradiated for 4 h under the same conditions without expelling the liquid (Figure S10d).

This process is depicted schematically in Figure 6. We hypothesize, that the hydrogel fibers depicted on Figures S17–S19 are stabilized by the hydrogen bonding network. In the dark state (Figure 6a), larger distance between the (*E*)-azobenzene fragments might enable accommodation of water and cargo molecules. The irradiation turns most of the fragments into more sterically demanding *Z* isomer (Figure 6b), which

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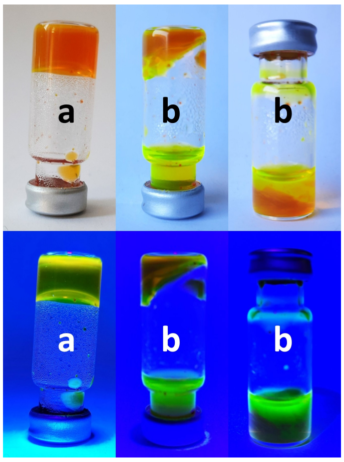


**Figure 5.** The fluorescent dye 5(6)-carboxyfluorescein (**2**) was added during the formation of a hydrogel (0.2 wt% of **1** in PBS at pH 7.4), and pictures were taken under ambient light or under UV irradiation. Sample **a** was equilibrated in darkness, sample **b** was irradiated for 4 h with red light (660 nm). In the latter case, the fluorescent cargo was predominantly released from the gel to the surrounding liquid and could be quantified.

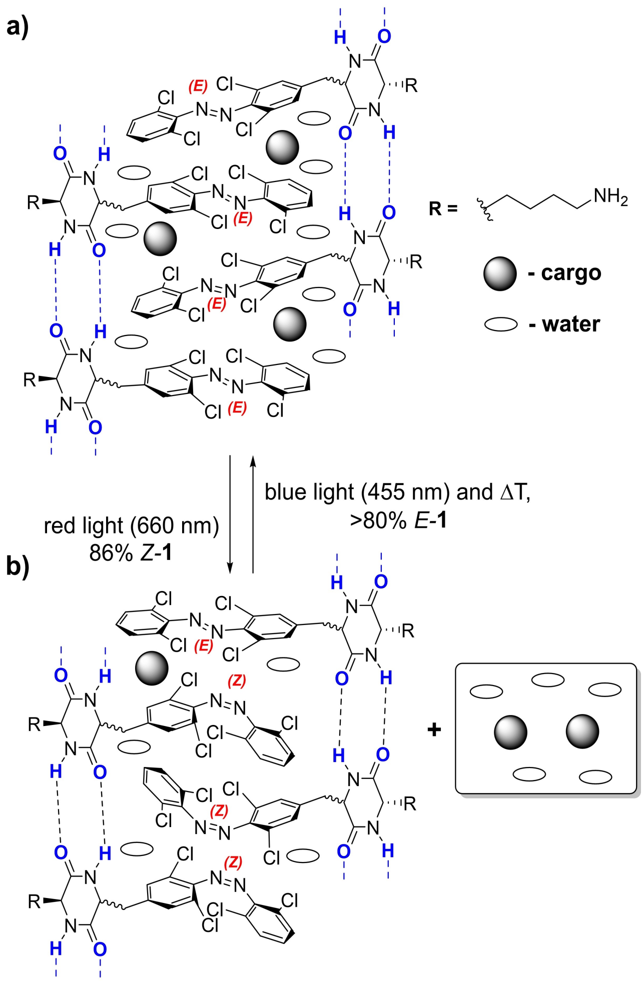


**Figure 6.** Schematic representation of the supramolecular fiber in the hydrogel loaded with cargo compounds (Figure 5). Hydrogel a) thermally equilibrated in the dark or b) irradiated with red light (660 nm).

results in ejection of the cargo and water from the fiber network.

Additional reasons for the observed macroscopic effect can be, say, light-induced polarity changes, or photomodulation of the helical pitch inside the supramolecular fibers.

Finally, we determined the cytotoxicity of **1** using cell viability assays (MTT assays). Human cancer cell line (HeLa) was treated with increasing concentrations of the gelator **1** (the 7:3 mixture), as well as each diastereomer **1a** and **1b** separately, to determine the respective $IC_{50}$ values. In each case, we have investigated the pure *E* isomers that form hydrogels in aqueous solutions, as well as the mixtures obtained upon irradiation (60 min) of the respective stock solutions with red light (660 nm). In all cases (Tables S7–S9), the $IC_{50}$ values were around or above 100 μM, indicating negligible toxicity (Figure S20) – apart from **1b**, where they oscillated around 10 μM (Figure S21).

To conclude, we have demonstrated synthesis and characterization of a new red-light-responsive supramolecular low-MW hydrogelator **1** based on a cyclic dipeptide bearing *ortho*-chlorinated azobenzene as the light-sensitive component. The hydrogelator undergoes efficient photoisomerization upon irradiation with 660 nm light, and thus is compatible with in vivo biological applications.[5] **1** formed mechanically stable hydrogels under physiologically relevant conditions (PBS buffer, pH 7.4) at exceptionally low concentrations (significantly below 1 wt%) – both as separated diastereomers, and as their mixture resulting directly from the synthetic process. Irradiation of the hydrogels with red light (660 nm) caused shrinking of the material with concomitant release of the aqueous buffer.

When the hydrogel has been quantitatively pre-loaded with fluorescent cargo (**2**), majority (up to 66%) of the guest was released to the aqueous solution upon red light irradiation, whereas in darkness the cargo remained firmly encapsulated inside the gel. The cytotoxicity of our material is generally low, and it demonstrated stability in reducing environment. Thus, the demonstrated "molecular syringe" is a promising system for light-induced drug release.

In the future, we will investigate techniques of injectable micro/nanogel formation from **1** and use bioactive cargo (anticancer or antimicrobial agents) in order to explore the therapeutic applications. Furthermore, we will explore the possibility of enantioselective synthesis for the photochromic amino acid **6**, as then it may find broader application for synthesis of photoresponsive peptides using solid-phase techniques.

## Acknowledgements

The authors gratefully acknowledge the financial support from Deutsche Forschungsgemeinschaft (DFG) – grants PI 1124/6-3, PI 1124/12-1, and GRK 2039. A.-L.L. is grateful to the Land of Baden-Württemberg for the support in form of "Landesgraduiertenstipendium". We want to thank Prof. Dr. Manfred Wilhelm and his group, especially Maxi Hoffmann, for their support in rheological measurements, Dr.-Ing. Heike Störmer and Volker Zibat (LEM KIT) for the assistance in electron microscopy data collection, as well as Prof. Dr. Hans-Achim Wagenknecht and Prof. Dr. Stefan Bräse (KIT Karlsruhe) for the infrastructural support of our research. We also gratefully acknowledge support by the KIT Publication Fund of the Karlsruhe Institute of Technology. Open Access funding enabled and organized by Projekt DEAL.

## 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:** smart materials · supramolecular hydrogels · therapeutic windows · photoresponsive soft materials

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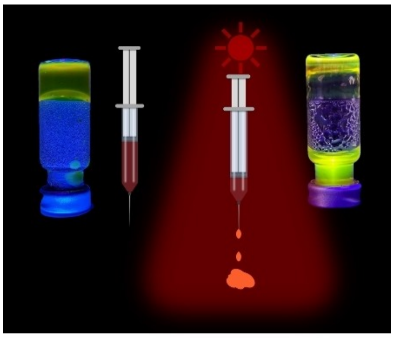
Manuscript received: July 18, 2023
Accepted manuscript online: August 22, 2023
Version of record online: ■■, ■■

**Red-y, steady, drop**: Molecular syringe is a peptide-derived photochromic hydrogel that can be loaded with cargo and then release the guest when biocompatible red light illuminates it under physiological conditions.



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