Aurones: Unexplored, Highly Efficient Visible-Light Photoswitches for Aqueous Medium

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ABSTRACT

The development of synthetically accessible photoswitches showing an efficient performance in aqueous medium has recently become an urgent task due to the rapid development of photopharmacology and novel biomedical applications. In response to this challenge, in this work, aurone derivatives are introduced for the first time as highly efficient visible-light photoswitches for aqueous medium. In general, aurones exhibit superior performance in water, including significantly higher quantum yields, compared with other indigoid photoswitches (hemithioindigo and hemiindigo). Especially remarkable are the half-lifes of the photoinduced *E*-isomers of aurones in water, reaching up to 7 years. Further modification of the aurone scaffold with substituents that increase water solubility does not affect most of the photoswitching characteristics and even improves some them. The highly advantageous property profile of the aurone photoswitches in water make them a perfect novel platform for the design of light-controllable molecules for bioapplications.

INTRODUCTION

The development of organic photoswitches with efficient performance in aqueous medium has recently gained emerging importance[1–10] in connection with applications in biology and medicine, including the rapidly growing fields of photopharmacology and fluorescence bioimaging.[11–16] However, the transfer of otherwise efficient photoswitches from organic solvents to aqueous medium very often interferes with the photochromism because of poor solubility, changed photophysics of the photoactive core and significantly altered characteristics of the molecular environment.[1] On the other hand, the introduction of water-solubilizing substituents in the photoswitchable scaffolds may result in the disruption of photochemical and biological properties of the molecule.[1] Along these lines, significant efforts are currently devoted to (i) the

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development of photoswitching-orthogonal strategies to reach good water solubility and (ii) finding novel water-soluble scaffolds with efficient photoswitching.[1–10]

Aurones are natural or synthetic flavonoids derived from the 2-benzylidenebenzofuran-3(2*H*)-one scaffold. Together with hemiindigo and hemithioindigo, aurones belong to the family of hemiindigoids (Scheme 1).[17] Hemiindigo and hemithioindigo are known for their remarkable photoswitching properties (Scheme 1), which have been utilized to provide photocontrol in molecular machinery, biological systems and supramolecular assemblies.[18] At the same time, the majority of aurone studies have been focused on their outstanding biological activities,[19–23] while photoswitching of these molecules has been reported just sporadically. Thus, in 2011, Bane and co-workers have described photoswitching of 4′-aminoaurone in chloroform.[24] In 2019, Qu and co-workers have utilized a 4′-alkoxyaurone fragment as a part of a bischromophoric photoswitch in toluene.[25] A single report of the photoswitching of aurones in polymer films is provided by Smokal in 2019.[26] However, to the best of our knowledge, photoswitching of aurones in aqueous medium has not been reported, so far.
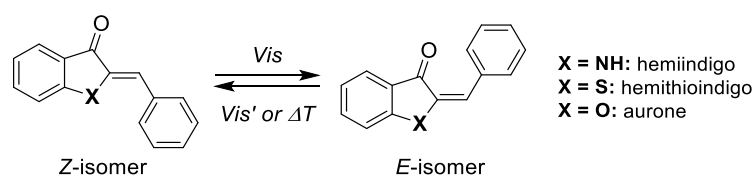

Scheme 1. Structures and photoswitching of hemiindigos, hemithioindigos and aurones.

Herein, we introduce aurones as a novel class of photoswitches for aqueous medium with a highly advantageous property profile. As a further development of the concept, a modification strategy of the aurone scaffold is described that gives access to the photoswitchable derivatives with excellent solubility in water and improved photostability without compromising most of the photoswitching characteristics.

RESULTS AND DISCUSSION

Aurone derivatives **1a**–**1h** were obtained in good yields as pure *Z*-isomers through the alumina-mediated condensation of 3-coumaranone with various aromatic aldehydes under mild conditions (Scheme 2).[27,28] The reaction proceeded without formation of side products and required only minimal purification by recrystallization to remove unreacted starting materials. Novel compound **1g** was identified and fully

characterized by 1D and 2D NMR spectroscopy, mass spectrometry and elemental analysis (*cf.* Supplementary information).
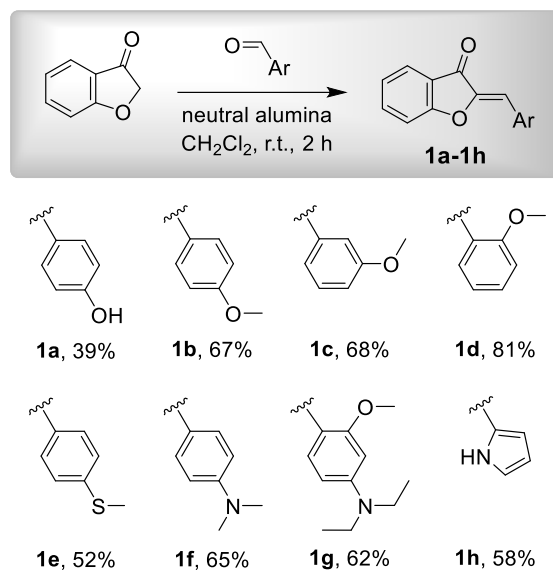
Scheme 2. Synthesis and structure of aurone derivatives **1a**–**1h**.

To establish the photoswitching properties of aurones in aqueous medium, their solubility has been assessed first. Thus, the pyrrole derivative **1h** shows good solubility in pure water, the derivatives **1a**–**1f** dissolve in water containing 10% of EtOH. Compound **1g** is the least soluble one and requires addition of 20% of EtOH. The long-wavelength absorption maxima of the aurones are located in the visible region of the spectrum except for the 3′-methoxy-substituted aurone **1c**, which absorbs in the UV range (Figure 1, Table 1). The comparison of the molar extinction coefficients of aurones **1a**–**1h** in water (Table 1) with the ones of the hemiindigo counterparts[29,30] revealed that aurones are better chromophores than hemiindigo in aqueous medium. Like hemiindigo and hemithioindigo, aurones are visible-light photoswitches (Table 1). The photoswitching performance of aurones significantly depends on the type and position of the substituents. Thus, hydroxy- and methoxy-substituted derivatives **1a**–**1d** as well as heterocyclic aurone **1h** show pronounced photoswitching. Remarkably, instead of *Z*–*E* isomerization, methylthio aurone **1e** undergoes [2+2] photocycloaddition upon irradiation at any applied wavelength (λ_{irr} = 375, 405, 420 nm) indicating formation of dimeric aggregates in aqueous medium even in a very diluted solution (for details see Supplementary information). Aurones **1f** and **1g** comprising alkylamino groups are not photochromic under the applied conditions. An interesting observation was made for derivative **1g** containing simultaneously the 2′-OMe group (supports photoswitching, *cf.* compound **1d**) and the 4′-NEt$_2$ substituent (suppresses photoswitching, *cf.* compound **1f**),

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whose combination in one molecule yielded a non-photochromic derivative **1g**. A possible reason for this is the increased donor–acceptor character of **1g** due to the conjugation with the alkylamino group, which leads to alternative charge-transfer excited states and different photochemical/photophysical de-excitation pathways than photoisomerization.
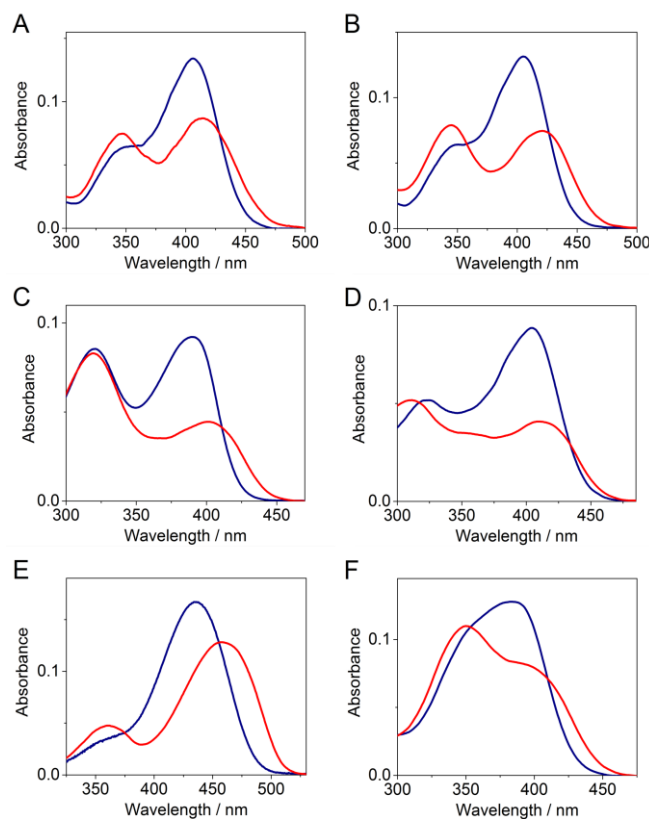

Figure 1. Absorption spectra of the *Z*-isomers (blue) and *E*-isomers (red) of photoswitchable aurones (A) **1a** in water with 10% (v/v) EtOH, (B) **1b** in water with 10% (v/v) EtOH, (C) **1c** in water with 10% (v/v) EtOH, (D) **1d** in water with 10% (v/v) EtOH, (E) **1h** in water, (F) **3** in water; in all cases $c = 5$ μM, 20 °C. For compounds **1b**–**1d**, the spectra of *E*-isomers were meausred experimentally, for compounds **1a**, **1h** and **3**, the spectra of *E*-isomers were calculated from the experimental data by the Fisher method.[31]

The forward *Z–E* isomerization of aurones **1a**–**1d**, **1h** typically occurs upon irradiation with violet light ($\lambda_{irr} = 405$ nm). However, for the derivatives **1a** and **1c**, the *Z–E* conversion is better upon irradiation with UV light ($\lambda_{irr} = 375$ nm). The best *Z–E* conversion of 81% was achieved for 4′-methoxy aurone **1b** and was comparable with the performance of hemiindigo and hemithioindigo (>80%).[1] For the other photochromic derivatives, conversions of 52–67% were reached. Similar *Z–E* conversions of 55–60% were reported for related aurones in chloroform, toluene and polymer films.[24–26] The backward *E–Z* photoswitching of aurones **1b**–**1d**, **1h** takes place upon irradiation with blue to green light ($\lambda_{irr} = 450$–520 nm). For compounds **1c** and **1h**,

the backward isomerization is close to quantitative. In the case of 4′-methoxy and 2′-methoxy derivatives **1b** and **1d**, the backward photoreaction proceeds with lower conversions (Table 1). For most aurones in aqueous medium, the quantum yields of both forward and backward photoisomerization (Table 1) are remarkably higher than those of the hemiindigo counterparts ($\phi_{Z\text{-}E}$ ca. 0.03 and $\phi_{E\text{-}Z}$ ca. 0.002)[29,30] This property makes aurones an attractive complementary alternative to hemiindigo photoswitches for applications in aqueous medium.

Table 1. Photochemical and photophysical properties of aurone derivatives **1a**–**1h** and **3** in aqueous medium.[a]

	$\lambda_{abs}(Z)$ / nm	$\varepsilon(Z)$ / L mol^{-1} cm^{-1}	λ_{abs} (E) / nm	$\varepsilon(E)$ / L mol^{-1}cm^{-1}	PSS^{fwd}/ %Z/E (λ_{irr}) [b]	PSS^{bkwd}/ %Z/E (λ_{irr}) [b]	$\phi_{Z\text{-}E}/\phi_{E\text{-}Z}$ / 10^{-2} [c]	ΔG^*/ kJ mol^{-1} [d]	$t_{1/2}$ / (25 °C) [e]
1a	406	25280	415 [f]	16390 [f]	33/67 (375)	n.d. [g]	0.09/n.d. [g]	81.93	36 s
1b	405	26195	421	14800	19/81 (405)	86/14 (505)	0.26/0.34	120.70 [h]	7 y [h]
1c	390	15380	401	8620	48/52 (375)	93/7 (450)	0.02/0.003	106.79 [i]	9.5 d [i]
1d	405	16995	409	8100	38/62 (405)	70/30 (455)	0.34/0.07	112.92	113 d
1e	413	27190	n.d. [j]	n.d. [j]	n.d. [j]	n.d. [j]	n.d. [j]	n.d. [j]	n.d. [j]
1f	488	30455	n.d. [k]	n.d. [k]	n.d. [k]	n.d. [k]	n.d. [k]	n.d. [k]	n.d. [k]
1g	516	47250	n.d. [k]	n.d. [k]	n.d. [k]	n.d. [k]	n.d. [k]	n.d. [k]	n.d. [k]
1h	435	31490	459 [f]	24735 [f]	38/62 (405)	97/3 (520)	0.06/0.06	100.51	18 h
3	383	25400	350, 390(sh) [f]	21855 [f]	22/78 (375)	90/10 (455)	0.23/0.10	n.d. [l]	> 1 y [l,m]

[a] Compounds **1h** and **3** in water, compounds **1a**–**1f** in water with 10% (v/v) EtOH, compound **1g** in water with 20% (v/v) EtOH. [b] Compositions of the photostationary states (PSS) at wavelengths producing the maximum conversion. [c] Photoisomerization quantum yields of the forward $\phi_{Z\text{-}E}$ (for **1a**–**1c**, **3**: λ_{irr} = 375 nm; for **1d**, **1h**: λ_{irr} = 405 nm) and backward $\phi_{E\text{-}Z}$ (for **1b**–**1d**, **3**: λ_{irr} = 455 nm; for **1h**: λ_{irr} = 520 nm) reactions. [d] Gibbs free activation energies for the thermal backward E–Z isomerization. [e] Half-lifes of the E-forms at 25 °C. [f] Calculated according to Fischer.[31] [g] Quantum yield of the backward E–Z photoisomerization could not be determined due to very fast thermal relaxation of the E-isomer. [h] Measured in water with 10% DMSO instead of 10% EtOH to record thermal relaxation kinetics at temperatures ≥ 85 °C (b.p. (EtOH) = 78 °C) because of a very long half-life of the E-isomer. [i] Measured in water with 10% DMSO instead of 10% EtOH to record thermal relaxation kinetics at temperatures ≥ 85 °C (b.p. (EtOH) = 78 °C) to prevent precipitation during 20 h-long measurements. [j] Compound **1e** underwent [2+2] photocycloaddition instead of Z–E isomerization. [k] Compound was not photochromic. [l] Was not possible to obtain full thermal relaxation kinetics because reduced stability of the compound at temperatures ≥ 80 °C. [m] The estimation of the half-life of the E-isomer was made based on comparison of the initial development of the thermal relaxation kinetics of **3** (before thermal destruction started) and the corresponding relaxation kinetics of compounds **1b** and **1c** recorded under identical conditions.

The half-lifes of the metastable *E*-isomers depend strongly on the type and position of the substituents. Thus, the *E*-isomer of 4′-hydroxy aurone **1a** rapidly relaxes back at ambient temperature (Table 1). The replacement of the 4′-OH with the 4′-OMe group in **1b** drastically increases the Gibbs free activation energy for the thermal *E*–*Z* isomerization making the photoisomer *E*-**1b** one of the most long-lived (7 years) metastable isomers in aqueous medium reported up to now (Table 1).[1-10] 3′-Methoxy and 2′-methoxy aurones *E*-**1c** and *E*-**1d** also showed pronounced half-lifes from 1.4 weeks to almost 4 months, which allowed to isolate and characterize their photoisomers (Figure 1, Table 1; for the isolation and characterization details see Supplementary information). The pyrrole derivative *E*-**1h** had a moderate half-life of 18 h, which precluded its isolation. To obtain the spectra of relatively short-living *E*-isomers of compounds *E*-**1a** and *E*-**1h** and evaluate the extent of the conversion in different photostationary states (PSS), the Fischer method was applied.[31] Comparison of the experimental spectra of the isolated *E*-isomers of methoxy aurones **1b**–**1d** with the spectra obtained for these compounds by the Fischer method (Figure S11, Supplementary information) confirmed a very good match of the calculated and experimental data. This observation indicated the applicability of the Fischer method for the characterization of the photoswitching of aurones, whose photoisomers are difficult to isolate. To assess the photostability of aurone photoswitches, cycling experiments were performed upon alternating irradiation of the solutions of **1b**–**1d**, **1h** by light of two different wavelengths for ten cycles (Figure S15, Supplementary information). For derivative **1a**, only the forward reaction was induced by light while the rapid backward switching occurred thermally. Thus, 4′-hydroxy aurone **1a** and heterocyclic derivative **1h** showed no sign of photodegradation after ten switching cycles. 4′-Methoxy aurone **1b** underwent slight degradation starting from the fourth switching cycle. The 2′-methoxy derivative **1d** started degrading after the third cycle, while the photodegradation of 3′-methoxy aurone **1c** started already after the first switching cycle.

As a next step, it was important to test the robustness of the photoswitching performance of aurones upon modification of the photoactive scaffold with additional substituents. To address this, the 4′-OMe aurone **1b** showing ideal photoswitching characteristics was derivatized with alkylamino substituents, which provided excellent solubility in pure water without the use of co-solvent. Thus, the modified compound **3** was obtained as a pure *Z*-isomer with 21% yield by *O*-alkylation of hispidol **2**[32] with 2-chloro-*N,N*-dimethylethylamine hydrochloride (Scheme 3). Product *Z*-**3** was identified and fully characterized by NMR spectroscopy, mass spectrometry and elemental analysis (*cf.* Supplementary information).
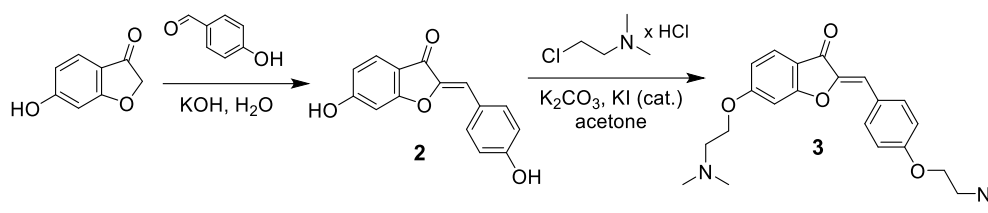
Scheme 3. Synthesis of aurone derivative **3**.

Importantly, the positions of substituents were selected in such a way that one of them had no effect on the chromophoric system in comparison with the parent compound **1b** (4′-position) while the second one acted as an auxochrome (6-position). Thus, as expected, modification of the heterocyclic core of **3** with an electron-donating substituent in the 6-position resulted in a blue-shift of the absorption maximum because of increase of the electron density on the carbonyl oxygen and consequent decrease of the donor–acceptor character of the chromophore (Figure 1F). Nevertheless, the photoswitching performance of **3** in comparison with the parent compound **1b** remained almost unchanged regarding the maximal conversion in the PSSs for both forward and backward reactions as well as the quantum yield of the forward *Z–E* isomerization (Table 1). As the only significant change in the photochemistry of **3** the quantum yield of the backward *E–Z* isomerization was ca. 3 times lower as compared with the one of **1b** (Table 1). Nevertheless, the quantum yield of 0.10 is still far superior to the values reported for hemiindigo in aqueous media (ϕ_{E-Z} ca. 0.002).[29,30] The Gibbs free activation energies for the thermal relaxation and half-life of the photoinduced isomer *E*-**3** could not be obtained because of the reduced thermal stability of the compound, which precluded kinetic measurements at ≥ 80 °C. However, the comparison of the initial development of the thermal relaxation kinetics of **3** (before the thermal decomposition started) and the corresponding relaxation kinetics of compounds **1b** and **1c** recorded under identical conditions allowed to estimate the half-life of the *E*-**3** at 25 °C to be more than one year. Remarkably, modification with alkylamino chains significantly improved the photostability of **3** in comparison with parent compound **1b**. Thus, derivative **3** showed no sign of photodegradation after 10 switching cycles whereas **1b** started slowly degrading from the fourth switching cycle (Figure S15, Supplementary information). The results obtained for aurone **3** clearly underlined the robustness of the photoswitching performance of aurones upon modification of the photoswitchable core even with the substituents changing the basic characteristics of the chromophoric system.

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CONCLUSIONS

In summary, aurones are introduced as a novel class of water-soluble photoswitches with highly efficient performance in aqueous medium. Synthetically easily accessible aurones **1b**–**1d** and **1h** act as visible-light photoswitches with the forward *Z*–*E* isomerization taking place upon irradiation with violet light and the backward *E*–*Z* isomerization occurring upon irradiation with blue to green light. However, for some derivatives, better forward *Z*–*E* conversion can be achieved with–UV light. Aurones show a very advantageous property profile in water, often exhibiting superior performance compared to hemithioindigo and hemiindigo analogues, including higher quantum yields and much longer half-lifes of the photoisomers. With the half-life of up to 7 years, the *E*-isomers of aurones belong to the most long-living photoinduced metastable forms in aqueous medium reported up to now. As a further development of the concept, a substitution pattern is provided that gives access to derivative **3** with excellent solubility in water and improved photostability without compromising most of the photoswitching characteristics. Overall, aurones represent a very promising new addition to the portfolio of water-soluble photoswitches and have broad application perspective in the areas requiring photoswitching in water, such as photopharmacology, biology, and green chemistry.

METHODS

General materials and methods are described in Supplementary information.

Synthesis

Known aurone derivatives **1a**–**1d**, **1f**, **1h** were characterized by comparison with the literature values of melting points and reported ^{1}H NMR spectroscopy data.[28,33-35] Compound **1e** was identified and characterized in our previous publication.[27] The full characterization for novel compounds **1g** and **3** is provided in Supplementary information.

General procedure for the synthesis of aurone derivatives 1a–1h

Synthesis of all aurone derivatives was performed according to M. Varma et al. [28]: 3-coumaranon (134 mg, 1.00 mmol) and the corresponding arylaldehyde (1.25 mmol) were dissolved in DCM (3 mL), then neutral alumina (3.25 g) was added, and the mixture was vigorously stirred for 3 h at r. t. Then alumina was filtered off and washed with DCM (3 x 15 mL). The solution was collected and evaporated *in vacuo*. The crude products were purified by recrystallisation from EtOH.

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Synthesis of (Z)-6-(2-(dimethylamino)ethoxy)-2-(4-(2-(dimethylamino)ethoxy)benzylidene)-benzofuran-3(2H)-one (3)

A mixture of hispidol **2** (0.39 mmol, 100 mg), K_2CO_3 (1.17 mmol, 162 mg) and KI (0.12 mmol, 19 mg) was suspended in acetone and stirred at 60 °C for 1 h. Then 2-chlorodimethylethylamine hydrochloride (0.59 mmol, 84 mg) was added to the mixture and the reaction was stirred at 60 °C for 3 days. After completion of the reaction, the precipitate consisting mainly of inorganic salt was filtered off. The remaining organic phase was evaporated to give a crude product. The crude was purified two times by gel-filtration chromatography on sephadex (MeOH) and recrystallized from acetone.

Photoisomerization studies

Photoisomerization studies of aurones were performed under UV-Vis spectroscopic control in 10 mm quartz cells, which were irradiated from top with LEDs of different wavelengths. The details of these experiments can be found in Supplementary information.

Calculations of the spectra of *E*-isomers by the Fischer method

The Fischer method was used to determine the extent of the *Z*–*E* conversion α upon irradiation in PSSs and to calculate the absorption spectra of pure *E*-isomers of aurone derivatives **1a**, **1h** and **3** with photoinduced forms, which were not possible to isolate. To prove the applicability of the Fischer method for the photoswitching of aurones, the calculated spectra of the *E*-isomers of compounds **1b**–**1d** with long-living photoinduced forms were additionally obtained and compared with the experimentally measured spectra of the isolated photoproducts. The experimental and calculated spectra closely overlapped with each other confirming the applicability of the Fischer method for the characterization of the photoswitching of aurones. The details can be found in Supplementary information.

Thermal stability of the photoisomers

Thermal dark *E*–*Z* relaxation kinetics of aurone derivatives were followed by UV-Vis spectroscopy at three different temperatures for each compound. The rate constants *k* were obtained from the exponential fitting of the thermal dark *E*–*Z* relaxation of the pre-irradiated photostationary mixtures of *E*- and *Z*-isomers at each temperature plotted at the wavelength at which only one of the isomers absorbs. The linear form of the Eyring

equation was applied to determine the values for ΔH^* and ΔS^* from the experimental kinetic data using the plot $\ln(k/T)$ *vs* $1/T$ (Eyring plot). Using the obtained ΔH^* and ΔS^* values, the Gibbs free activation energies for the thermal backward *E–Z* isomerization and the half-lifes of the *E*-isomers at 25 °C were calculated. The details can be found in Supplementary information.

Photoisomerization quantum yields

The quantum yields for the forwar and backward photoisomerization of aurones were obtained from the UV-Vis spectroscopy data using the initial slope method. The details can be found in Supplementary information.

AUTHOR CONTRIBUTIONS

D. V. B. designed the project, carried out the experiments, analyzed the data and wrote the manuscript.

COMPETING INTERESTS

The author declares no competing interests.

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