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Heterocyclic Hemipiperazines: Water-Compatible Peptide-Derived Photoswitches

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Abstract: Hemipiperazines are a recently discovered class of peptide-derived molecular photoswitches with high biocompatibility and therapeutic potential. Here, for the first time we describe photochromism of heterocyclic hemipiperazines. They demonstrate long thermal lifetimes, and enlarged band separation between photoisomers. Efficient photoisomerization occurs under aqueous conditions, although with a need for organic co-solvent. Bidirectional switching with visible light is observed for an extended aromatic system.

Introduction

Molecular photoswitches[1] are "antennas" that enable conversion of light energy into reversible changes of molecular geometry, polarity, or rigidity[2] – principally due to reversible electrocyclizations,[3] or *E*/*Z*-isomerization of a double bond.[4] This effect has been broadly used to design smart materials[5] that reversibly change their properties upon stimulation with light - actuators,[6] liquid crystals,[7] hydrogels,[8] or porous materials[9] including MOFs.[10] Molecular photoswitches are also used for solar thermal energy storage.[5a,11] Modulating behavior of biological systems is achieved with photoswitchable oligonucleotides,[12] peptides[13] and proteins,[14] saccharides,[15] or bioactive small molecules.[16] The particular case is photopharmacology,[17] where pharmacophores decorated with photochromic motifs exhibit activity photomodulation, which may be prospectively adapted for therapeutic applications.[18]

Well-known photochromic structures based on azobenzenes,[19] spiropyrans,[20] or diarylethenes,[21] have been more recently complemented with indigoids,[22] donor-acceptor Stenhouse adducts,[23] imines[24] and arylhydrazones,[25] diazocines,[26] or dihydropyrenes,[27] as well as a range of emerging photoswitches.[28] However, they show numerous limitations that are particularly inconvenient in more complex biological setups – such as incompatibility with water or intracellular reducing components, low photoconversions, or thermal instability. Together with their structural mismatch with the majority of established pharmacophores, all this stimulates development of new classes of biomolecule-mimicking photochromic systems.

We have previously reported a novel class of biocompatible molecular photoswiches – hemipiperazines (HPI) – based on *E*/*Z*-isomerization of the 3-benzylidene-2,5-diketopiperazine scaffold, which is derived from cyclic dipeptides.[29] HPI photoisomerization was successfully applied for substantial activity photomodulation in a low-nM antimitotic agent plinabulin and its derivatives with visible light. As cyclic dipeptide derivatives are ubiquitous bioactive substances and pharmacophores,[30] this discovery opens up new avenues in photopharmacology and photocontrol of biological systems. However, due to substantial spectral overlap of photoisomers, photoswitching in carbocyclic HPIs remains far from quantitative. Efficient photoconversions are only possible for HPIs bearing strongly electron-donating substituents, which in turn increase their sensitivity on photooxidative degradation. Such limitations have been in the past successfully addressed in other photochromic scaffolds by replacement of carbocyclic substituents with heteroaryl analogues,[31] which favorably modified their photophysical properties, including bathochromic absorption shift and enhanced spectral separation of isomers, or polarity.[32] Therefore, we decided to apply this strategy to the original carbocyclic HPI design. In particular, we wanted to investigate pyrrole, furane, and thiophene substituents, that were previously implemented in hemithioindigo switches,[31b] as well as a representative subset of their regioisomers and benzologues.

Here, for the first time we demonstrate systematic investigation of the photochromism in heteroarylidene hemipiperazines (hHPI) (Figure 1). They exhibit more efficient photoconversions, improved band separation and red-shifted absorption in comparison with their carbocyclic prototypes.[29] That, in combination with high thermal stability and efficient switching under aqueous conditions, renders the heterocyclic HPI photochrome attractive for applications in biological context, like photopharmacology systems or photomodulation of biopolymers.

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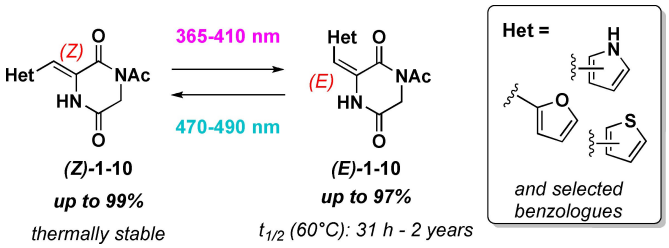

Figure 1. Heteroarylidene-substituted 2,5-diketopiperazines **1**–**10** are novel molecular photoswitches, operational also in water-containing media. They belong to a recently identified class of peptide-derived photochromic hemipiperazines (HPI).[29]

Results and Discussion

A representative panel of heteroarylidene-substituted 2,5-diketopiperazines **1**–**10**, including 5-membered-ring heterocycles and their benzologues, has been synthesized by base-catalyzed condensation of the respective heteroaromatic aldehydes with 1,4-diacetyl-2,5-diketopiperazine **11**. The products **1**–**10** were isolated as the *Z*-isomers with the yields between 27% and 89% (Figure 2a), ranging into gram scale (>2 g of **6**), and the absorbance maxima in the range of 340–400 nm (Figure 3a). The Z-selectivity of this reaction has been previously explained by the Zimmerman-Traxler model.[33] We have confirmed the *Z*-configuration in selected cases with NOESY NMR spectra (Figures S15, S19, S24, S27, S31, and S34). The newly formed double bond undergoes reversible photoinduced isomerization (Figure 1).

Upon irradiation of the thermodynamically stable *Z*-isomers with UV light (365 nm), the substances **1**–**10** have been equilibrated to achieve photostationary states (PSS) with large excess (up to 97%) of the respective *E*-isomers (Table 1, Figures S1 and S5). Due to extraordinarily high thermal stability at room temperature, their lifetime had to be determined at 60 °C (in MeCN). The half-life at this temperature spans between 31 h and two years, depending on the substitution pattern (Figures S6 and S7, Table S2). Thus, we deem all the *E*-isomers of **1**–**10** thermally metastable at ambient conditions. Each isomer can be isolated and separately characterized at room temperature (Figure S10).

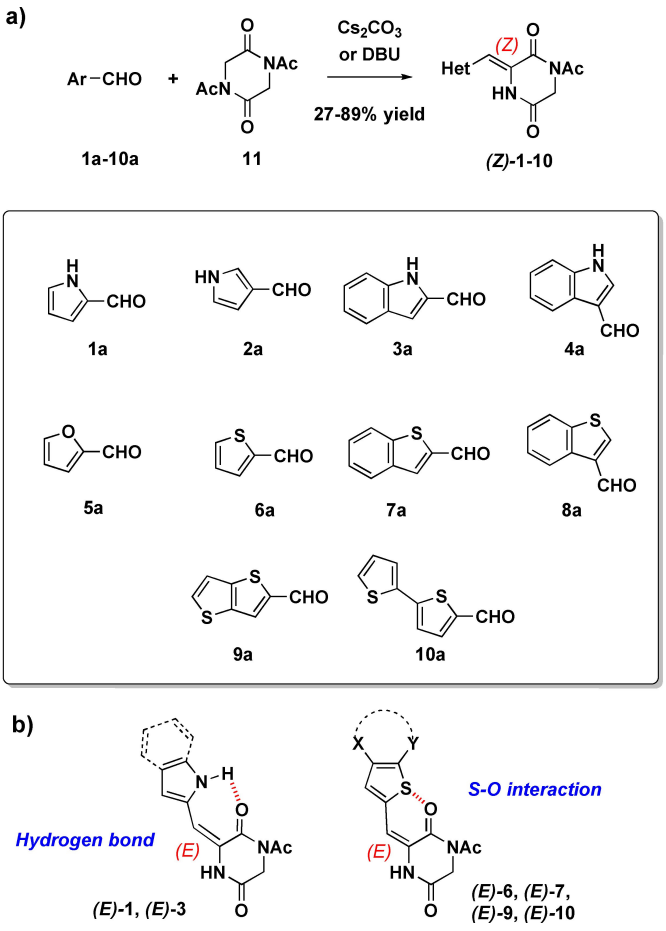

Figure 2. a) Synthesis and structure of the heteroarylidene-substituted 2,5-diketopiperazines (heterocyclic hemipiperazines, hHPI) **1**–**10** investigated in this report; b) intramolecular interactions that occur in the *E*-isomers of indicated heterocyclic HPIs and may moderately increase their thermal stability.

Lifetime differences observed between the 2- and the 3-substituted pyrrole-containing HPIs **1** and **2**, as well as their benzologues **3** and **4** (Table S2), prompted us to analyze the eventual influence of stabilization of the *E*-isomer provided by supramolecular interactions (depicted on Figure 2b) such as hydrogen bonding for **1** and **3**, (important in heterocyclic hemithioindigo switches[31b]), or – in sulfur-containing hHPIs – a

Table 1. Photoisomer composition (percentage of the *E*-isomer) at the photostationary states determined for the irradiation of compounds **1**–**10** with selected wavelengths in the range 365–490 nm (solutions in DCM, determined with HPLC).

Compound number	Photoisomer composition (% *E*)					
	356 nm [UV]	410 nm (violet)	430 nm (violet)	455 nm (blue)	470 nm (blue)	490 nm (cyan)
1	80	21	4	2	<1	–
2	39	3	<1	<1	–	–
3	97	94	88	56	32	39
4	80	26	22	6	3	7
5	44	2	2	-	–	–
6	70	10	8	4	–	–
7	61	9	5	3	–	–
8	63	17	7	6	–	–
9	75	23	9	6	5	–
10	80	80	68	48	38	25

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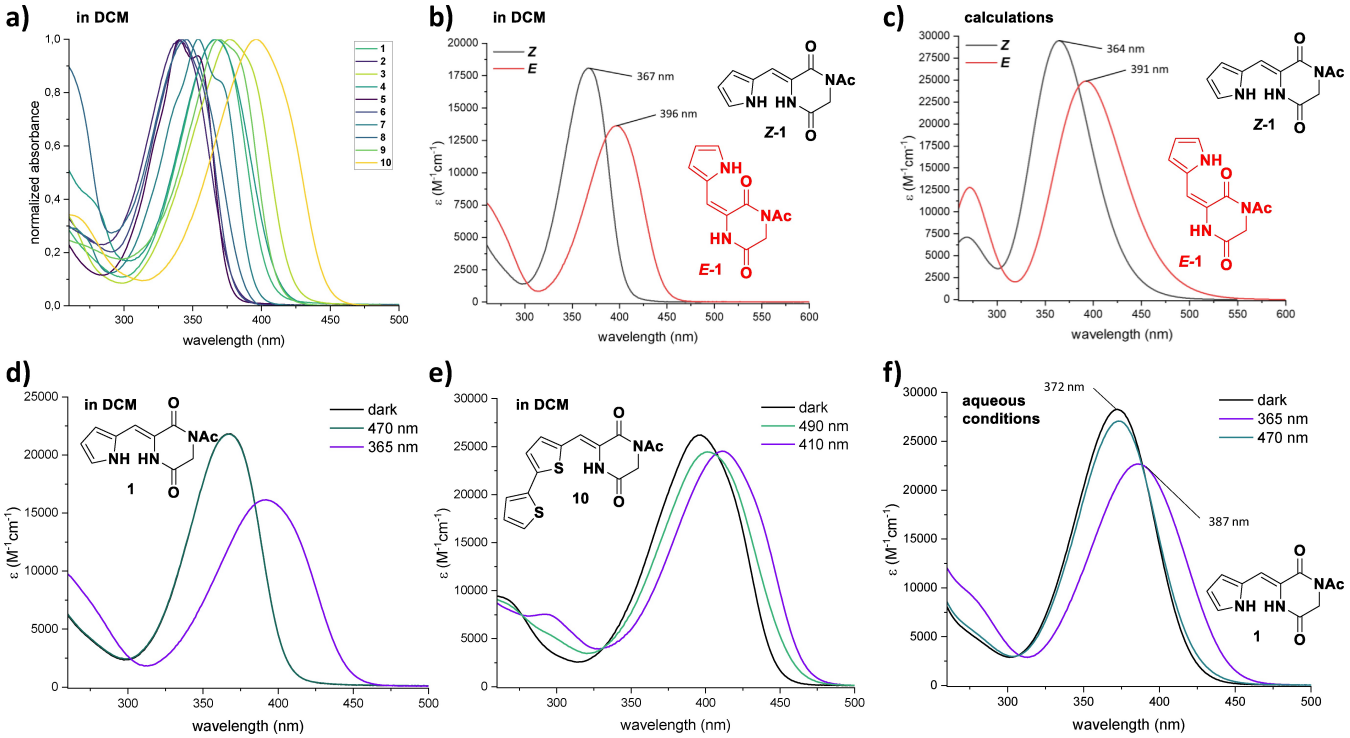

Figure 3. Photophysical properties of heterocyclic hemipiperazines. a) absorption spectra of the *Z*-isomers of **1**–**10** (80 μM in DCM); b) the distance between the absorption maxima for purified *Z*-**1** and *E*-**1** (29 nm peak separation) in DCM; c) theoretical calculations of the UV-Vis spectra for the photoisomers of **1**, using B3LYP-GD3BJ/6-311G(d,p) PCM(DCM) level of theory; d–f) representative examples of the photochromism of hHPI - UV-Vis spectra in darkness and at the two selected photostationary states with highest photoconversions to the *Z*- and *E*-isomer : d) photochromism of **1** (80 μM **1** in DCM) - $PSS_{365\ nm}$: 80 % *E*-**1**, $PSS_{470\ nm}$: > 99 % *Z*-**1** (the curve overlaps with the initial dark state); e) photochromism of **10** (80 μM **10** in DCM) switchable with visible light - $PSS_{410\ nm}$: 80 % *E*-**10**, $PSS_{490\ nm}$: 75 % *Z*-**10**; f) photochromism of **1** under aqueous conditions (80 μM **1**, 10 mM GSH, 5 mM TCEP, 75 % PBS pH 7.4, 25 % DMSO) - $PSS_{365\ nm}$: 88 % *E*-**1**, $PSS_{470\ nm}$: 84 % *Z*-**1**.

geometrically feasible orbital overlap between heterocyclic sulfur and the carbonyl group (observed in calculated LUMO + 1 orbitals, Figures S51 and S59). The presence of moderately strong hydrogen bonding has been confirmed using difference in chemical shifts of the involved hydrogen atoms in DMSO and $CDCl_3$ (Table S3). Their strength has been computationally determined to be 9.674 kcal/mol (**1**) and 9.867 kcal/mol (**3**). Moreover, natural bond orbital (NBO) analysis (see Supporting Information pages 126–136) showed an O···H Wiberg bond index of 0.05 and 0.046, which is slightly smaller than the values 0.08–0.07 calculated for the heterocyclic indigoids.[31b] However, given the vast thermal stability of all the investigated *E*-isomers, the discussed supramolecular interactions can only have moderate influence on the overall thermal stability.

Next, we have investigated the photochromism of compounds **1**–**10** (Figures 3d–f and S1). The *E*/*Z*-ratios in the respective photostationary states (PSS) have been determined with HPLC using wavelengths of the respective isosbestic points, upon irradiation of samples (initially isolated as pure Z-isomers) in DCM (Table 1, Figure S5). These results were also corroborated in selected cases with ^{1}H NMR analysis of the of samples irradiated in d^6-DMSO (Figure S4). In diluted DMSO solutions, we have often observed photodegradation, which was however suppressed upon addition of ascorbic acid.

Irradiation of **1**–**10** with UV light (365 nm) resulted in the highest ratio of the *E*-isomer (in most cases, between 60 % and 80 %). Its percentage is then significantly reduced upon further treatment of the same samples with violet up to cyan light (410–490 nm), often reaching below 5 % of the *E*-form (Figures 3d, S1 and S5). Separation of the isomer absorption maxima in the heterocyclic HPIs **1**–**10** can reach almost 30 nm, which results in much larger span between the photoisomer ratios in the extreme photostationary states (Figures 3b, S10) in comparison to the carbocyclic HPIs (maximally 12 nm band separation range[29]). Due to the extended π-electron system, the compound **10** can be bidirectionally switched with visible light frequencies (Figure 3e).

Furthermore, photoisomerization of all the compounds **1**–**10** has been performed upon 10 cycles (alternate irradiation with 365 nm and 470 nm) in DCM in presence of ascorbic acid (100 equiv.) that prevents degradation. Slight fatigue (below 2 % upon 10 cycles) was only observed for the compounds **4** and **7**, while the compound **5** was more prone to photodegradation (10 % decay upon 10 switching cycles under these conditions) (Figure S8). Overall, the majority of investigated photoswitches is fatigue-resistant upon multiple switching cycles. Prolonged exposure to UV light (> 240 min) ultimately results in complete photodegradation to a mixture of unseparable and unidentified products (Figure S9).

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Another important feature for potential biological applications is efficient photoconversion under aqueous conditions, especially in presence of reducing agents (like glutathione that occurs inside living cells in millimolar concentrations). This has been demonstrated here for the compound **1** (Figures 3f and S2). Like in case of carbocyclic HPIs, here we have observed that glutathione does not cause degradation of heterocyclic HPIs.[29] We have confirmed, that 10 mM glutathione does not degrade compound **1** upon prolonged exposure (15 h, Figure S2d). And its stability upon multiple switching cycles under aqueous conditions is satisfactory – in presence and in absence of glutathione (96–99% upon 10 full photoisomerization cycles, Figure S3).

The compounds **1**–**10** show little solvatochromism, slightly more pronounced only for the compounds **2** and **3** (Figure S11). We have also determined the quantum yield of photoisomerization ($Z \rightarrow E$, 12%) for the compound **3** (Figure S12), which is comparable with other photochromic systems.[34]

The experimentally observed photochromism of **1**–**10** has been supported with theoretical calculations of the molecular orbital energy and simulated electronic spectra. There, we have implemented the B3LYP-GD3BJ/6-311G(d,p) PCM(DCM) level of theory, successfully applied beforehand for calculations of the properties of carbocyclic hemipiperazines (Figures 3c, S40–S59).

Conclusion

In conclusion, we have demonstrated that heteroarylidene substitution of the cyclic dipeptide scaffold leads to heterocyclic hemipiperazine (hHPI) photoswitches, which undergo efficient photoconversions, also under reductive aqueous conditions, with UV light to the thermally metastable *E*-isomers. They can be conveniently isolated by column chromatography, stored, and often quantitatively switched back to the thermostable *Z*-isomers with cyan light (470–490 nm), while at room temperature in darkness they enjoy almost indefinite shelf lifetime. The extended aromatic system in hHPI **10** enables bidirectional switching within the visible light range (410/490 nm). However, clear design rules for the relationship between molecular structures and absorption maxima cannot be formulated at this stage. Efficient photoconversions occur due to enhanced separation of the absorption maxima between respective photoisomers, comparing to the carbocyclic analogues reported earlier on. To the best of our knowledge, it is the first systematic investigation of photochromism in heterocyclic hemipiperazines.

Combination of the aforementioned features renders this class of photoswitches attractive for applications in biological context, like photopharmacology systems or photomodulation of biopolymers. The heterocyclic hemipiperazine chromophore occurs in numerous bioactive natural products, such as barettin,[35] dipodazine,[36] or phenylahistin.[37] And it is structurally similar to the broad variety of bioactive indole- or imidazole-bearing cyclic dipeptides (i.a. brevianamide F, tyrprostatins, thaxstomins), biosynthetically derived from tryptophan or histidine, respectively.[30b] Our report indicates, that these and other heteroarylidene-substituted 2,5-diketopiperazines are attractive potential targets for controllable reversible bioactivity photomodulation.

Apart from structurally determined biological applications, heterocyclic hemipiperazines will be likely applied in new generations of smart materials, such as light-triggered actuators, mesophases, porous materials, soft materials, or nanostructures, as already happened for almost every class of emerging molecular photoswitches reported in the last two decades.[1b]

In the future, we will explore the factors that may bathochromically shift the absorption maxima and enable efficient bidirectional switching with red-shifted wavelengths of light, in order to increase compatibility with more complex biological systems, such as tissues or whole organisms. We will also investigate photopharmacological applicability of this new chromophore.

Experimental Section

Synthesis of hemipiperazines 1–10: 1,4-diacetylpiperazine-2,5-dione (**11**) (300 mg, 1.51 mmol, 1.25 equiv.) was dissolved in dry DMF (0.20 M) under an argon atmosphere. The respective aldehyde **1a**–**10a** (1.00 equiv.) was dissolved in the mixture and DBU (1.10 equiv.) was added. The mixture was stirred for 16–18 h under an argon atmosphere at room temperature. The reaction mixture was subsequently poured on ice-cold water (10 times the volume of DMF) and the resulting precipitate was filtered off. The crude product was finally purified either via column chromatography or recrystallization, resulting in pure *Z*-isomers of the hemipiperazines with 27%–89% yields.

Isolation of the E-isomers of hemipiperazines 1–10: The respective *E*-isomers were isolated by irradiating a solution of the respective *Z*-isomer in DMSO at 365 nm for 1 h. This mixture was poured on ice-cold water, the resulting precipitate was filtered off, and purified via column chromatography. Alternatively, the irradiated solution was directly subjected to purification via HPLC, the respective fractions were combined and extracted, using EtOAc. The combined organic layers were then washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and the volatiles were removed *in vacuo* to afford the pure *E*-isomers.

UV-Vis absorption spectra at the photostationary states (PSS): Compounds **1**–**10** were each dissolved in CH_2Cl_2 with a final concentration of 80 μM. The absorption spectra ($d = 5$ mm) of the non-irradiated samples were measured first. The samples were then irradiated with wavelengths in the range of 365 nm–490 nm for defined time intervals (10 s–4 min), until the PSS was reached (10 s–40 min). Then the absorption spectra were recorded again.

Determination of the *E*/*Z* isomeric ratio at the photostationary states (PSS): 1 mM stock solution in CH_2Cl_2 (containing 1 vol% DMSO to help dissolution) of each compound **1**–**10** was irradiated with 365 nm until the PSS was reached. Afterwards, five individual samples were taken from this stock solution. These were then further irradiated with either 410 nm, 430 nm, 455 nm, 470 nm or 490 nm, to demonstrate the back-switching capability of the presented compounds. The solvent was subsequently removed *in vacuo*, the residual solids re-dissolved in MeCN and finally analyzed via HPLC (Figure S4).

Thermal stability determination of the E-isomers of hemipiperazines 1–10: Compounds **1**–**10** were dissolved in MeCN with a

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concentration of 1 mM. The solutions were irradiated with 365 nm until the PSS was reached (monitored via HPLC) and then incubated at 60 °C for a total of 219 h (173 h for compound **5**, 289 h for compound **8**). During this time, small aliquots of 75 µL were taken, diluted with 75 µL of MeCN and analysed via HPLC to follow the decrease in amount of *E*-isomer present in the isomeric mixture.

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Conflict of Interest

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: hemipiperazines · heterocycle · photochemistry · photochromism · photoswitch

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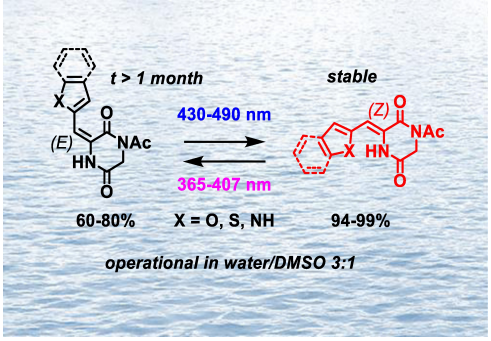

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Photoswitching in presence of water: decoration of cyclic dipeptides with heteroarylidene substituents produces novel biocompatible molecular photoswitches. They show high thermal stability, and are operational under aqueous conditions with an organic co-solvent. Extended heteroaromatic system enables bidirectional switching with visible light.

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