

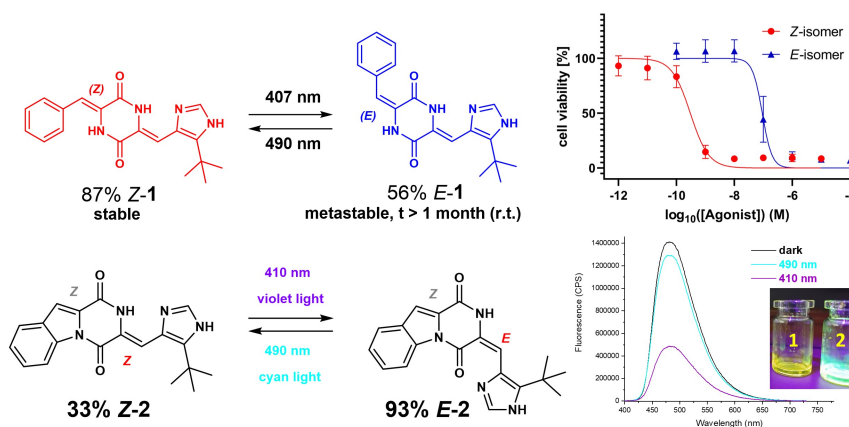
Hemipiperazines: peptide-derived photoswitches with low-nanomolar toxicity

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Cyclic dipeptides (CDP) are common structural motifs in biology, potent pharmacophores, and important constituents of numerous supramolecular systems based on hydrogen bonding.[1] Light-triggered photomodulation of their properties, e.g. upon merger with molecular photoswitches,[2,3] opens the way for photopharmacology applications, or producing smart materials.

Upon investigation of light-triggered release of CDP drugs from photochromic supramolecular hydrogels [4], we have discovered that plinabulin (**Z-1**) – a low-nM antimetabolic agent - reversibly photoisomerizes to its thermally stable photoisomer (**E-1**) with significantly lower activity, which can be isolated and used as a photoactivated pro-drug.[5] Moreover, its previously unreported photochromic system – hemipiperazine – constitutes a new class of molecular photoswitches [2,3] with broad application potential, ranging from smart materials to photopharmacology. We have examined basic photophysical properties of the isolated hemipiperazine photochrome.[5,6] Finally, the “locked” plinabulin **2** exhibits enhanced fluorescence, and reversible photomodulation of the fluorescence level upon photoisomerization - which may in turn find applications e.g. in super-resolution microscopy.[5]



[1] C. Balachandra, D. Padhi, T. Govindaraju *ChemMedChem*. **2021** *16*, 2558-2587.

[2] Z. Pianowski *Chem. Eur. J.* **2019**, *25*, 5128-5144.

[3] Z. Pianowski (Ed.) *Molecular photoswitches. Chemistry, properties, and applications 2022*, Wiley-VCH.

[4] J. Karcher, Z. Pianowski, *Chem. Eur. J.* **2018**, *24*, 11605-11610; Karcher J., et al. *RSC Adv.*, **2021** *11*(15), 8546-8551.

[5] S. Kirchner, A.-L. Leistner, P. Gödtel, A. Seliwjorstow, S. Weber, J. Karcher, M. Nieger, Z. Pianowski *Nat. Commun.* **2022**, *13*, 6066.

[6] P. Gödtel, J. Starrett, Z. Pianowski *Chem. Eur. J.* **2023**, *29*, e202204009