university of groningen

The chemistry of Photopharmacology

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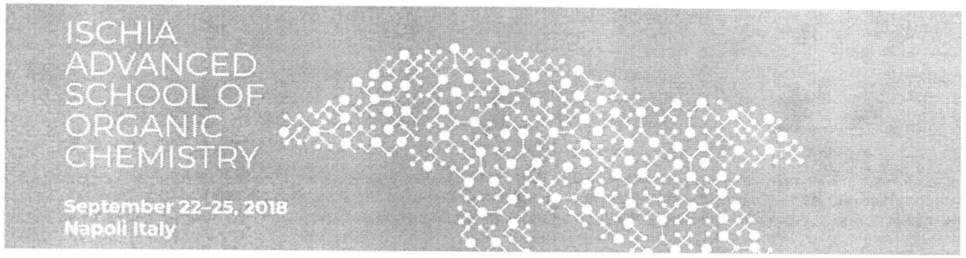
www.szymanski-lab.com
www.photopharmacology.nl



Photocontrol of biological processes

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- Light shows a great degree of orthogonality towards most elements of biochemical systems.
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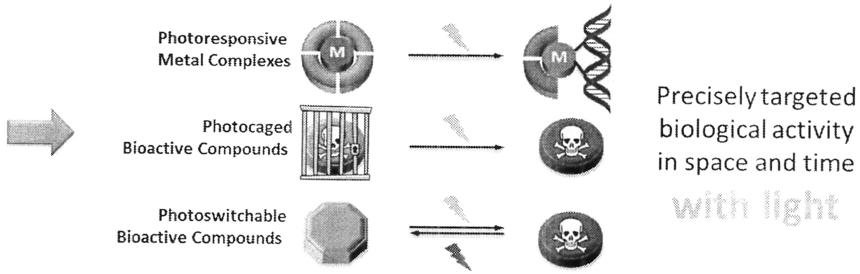
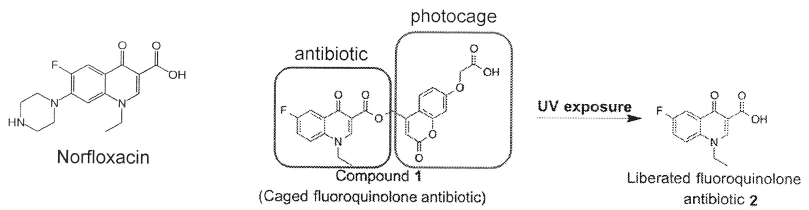


1) M. W. H. Hoorens, W. Szymanski, Trends. Biochem. Sci, **2018**, *43*, 567 **2)** F. Reessing, W. Szymanski, *Curr. Med. Chem.* **2017**, *24*, 4905-4950; **3)** W. Szymanski, J. M. Beierle, H. Kistemaker, W. Velema, B. L. Feringa, *Chem. Rev.* **2013**, 6114-6178; **4)** A. A. Beharry, G. A. Woolley, *Chem. Soc. Rev.* **2011**, *40*, 4422; **5)** G. Mayer, A. Heckel, *Angew. Chem. Int. Ed.* **2006**, *45*, 4900–4921; **6)** A. Deiters, *ChemBioChem* **2010**, *11*, 47–53.

Photocaging: applications



A

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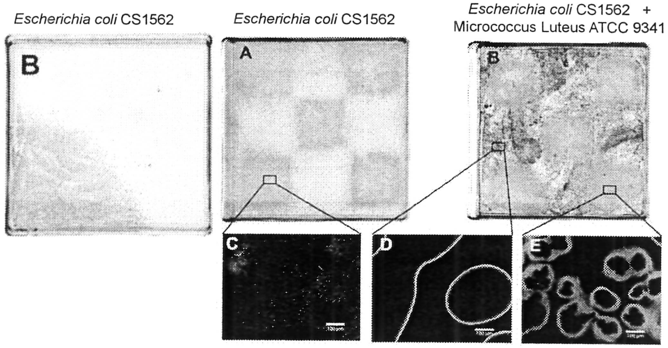
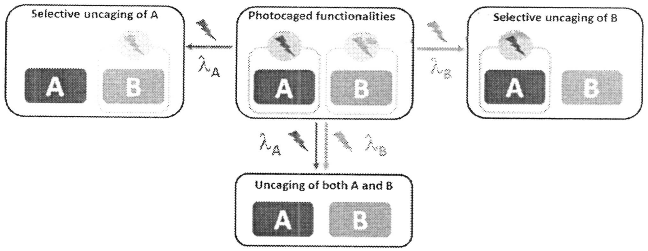
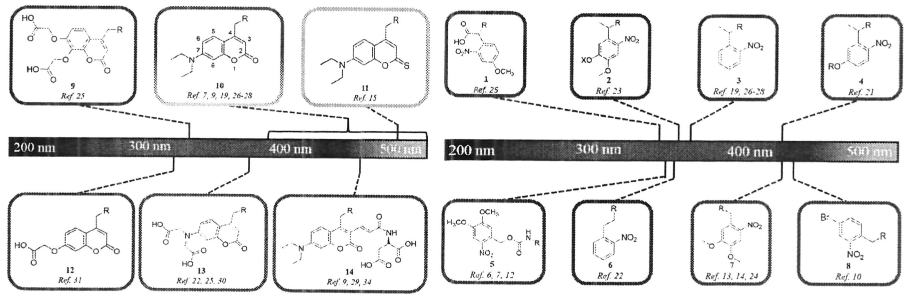


W.A. Velema, J. P. van der Berg, W. Szymanski, A. J. M. Driessen, Ben L. Feringa, *Org. Biomol. Chem.* **2015**, *13*, 1639-1642.

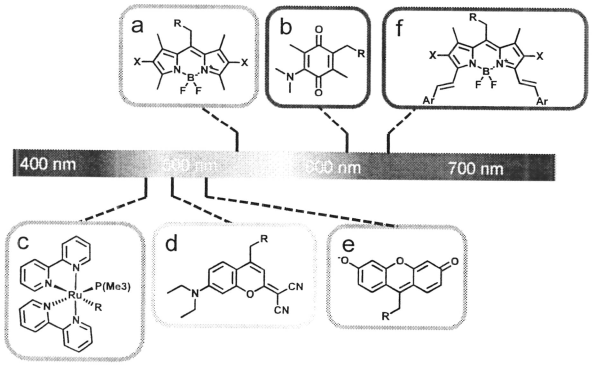
Orthogonal Photocaging





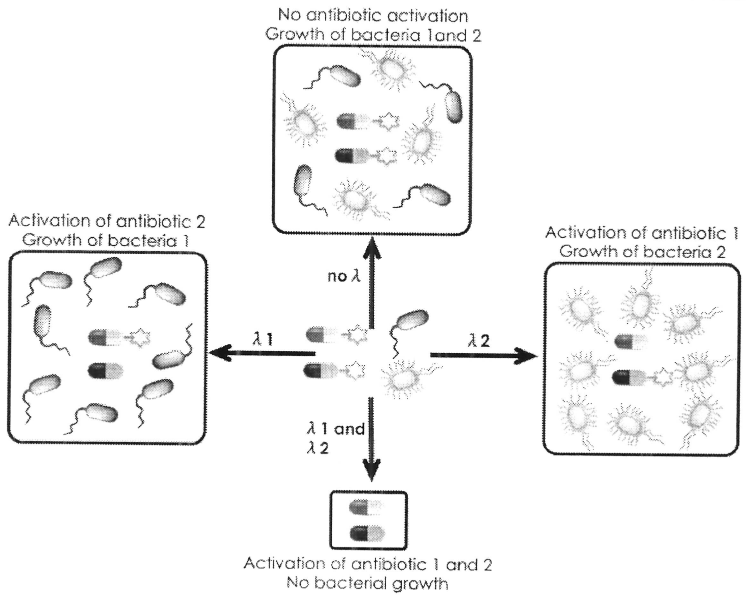
M. J. Hansen, W. A. Velema, M. M. Lerch, W. Szymanski, B. L. Feringa *Chem. Soc. Rev.* **2015**, *44*, 3358-3377.

Visible light-responsive cages



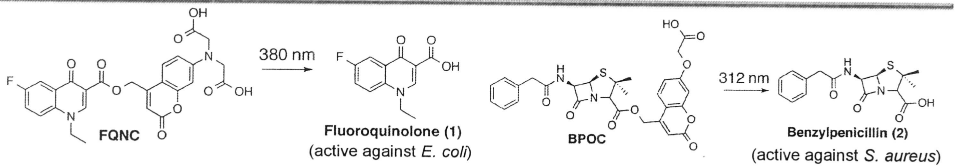
a) Umeda, *et al. ACS Chem. Biol.*, **2014**, 9, 2242; Rubinstein *et al. Chem. Comm.*, **2015**, *51*, 6369; Slanina *et al. J. Am. Chem. Soc.* **2017**, *139*, 15168; Goswami *et al. J. Am. Chem. Soc.*, **2015**, 137, 3783;
b) Carling *et al. Chem. Sci.*, **2016**, *7*, 2392; Wang, X.; Kalow, J. A.; *Org. Lett.* **2018**, *20*, 1716
c) Filevich *et al. Photochem. Photobiol. Sci.*, **2013**, *12*, 1565; Howerton *et al. J. Am. Chem. Soc.* **2012**, *134*, 8324
d) Fouriner *et al. Chem. Eur. J.* **2013**, *19*, 17494
e) Sebej *et al. J. Org. Chem.* **2013**, *78*, 1833
f) Peterson *et al. J. Am. Chem. Soc.* **2018**, *23*, 7343-7346

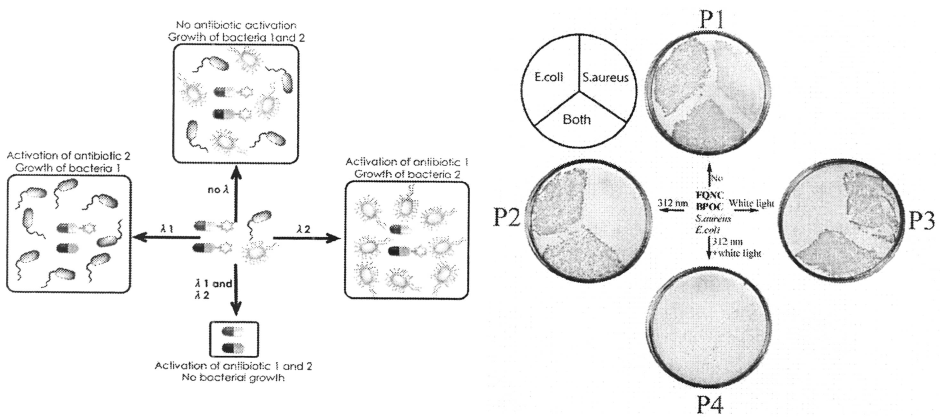
Photocaging groups II: applications



Willem A. Velema, Jan Pieter van der Berg, Wiktor Szymanski, Arnold J. M. Driessen, Ben L. Feringa, *ACS Chem. Biol.* **2014**, *9*, 1969-1974.

Photocaging groups II: applications





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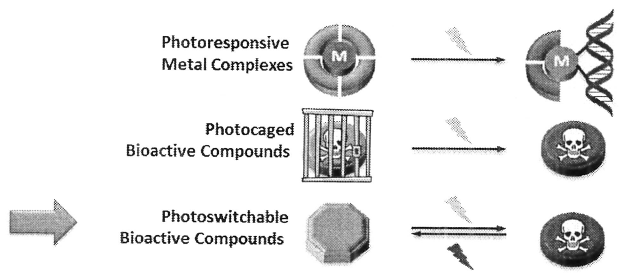

Precisely targeted biological activity in space and time with light

1) F. Reessing, W. Szymanski, *Curr. Med. Chem.* **2017**, *24*, 4905-4950; **2)** W. Szymanski, J. M. Beierle, H. Kistemaker, W. Velema, B. L. Feringa, *Chem. Rev.* **2013**, 6114-6178; **3)** W. Szymanski, D. Yilmaz, A. Kocer, B. L. Feringa, *Acc. Chem. Res.* **2013**, *46*, 2910-2923; **4)** A. A. Beharry, G. A. Woolley, *Chem. Soc. Rev.* **2011**, *40*, 4422; **5)** G. Mayer, A. Heckel, *Angew. Chem. Int. Ed.* **2006**, *45*, 4900–4921; **6)** A. Deiters, *ChemBioChem* **2010**, *11*, 47–53.

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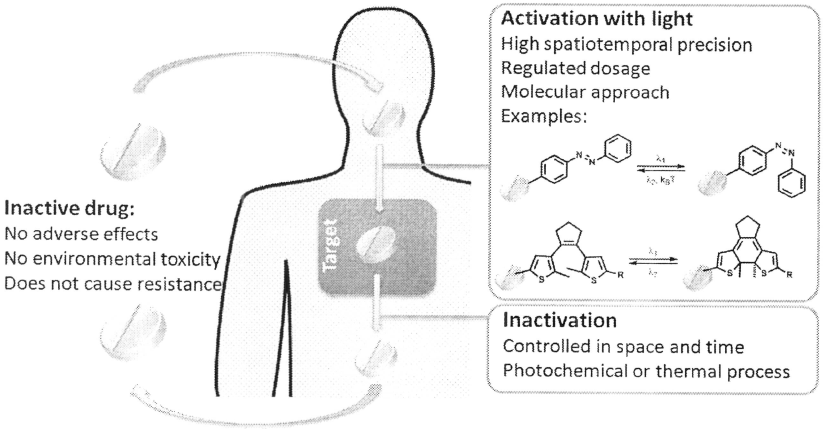
Photopharmacology



W.A. Velema, W. Szymanski, B. L. Feringa, *J. Am. Chem. Soc.* **2014**, *136*, 2178
J. Broichhagen, J .A. Frank, D. Trauner, *Acc. Chem. Res.* **2015**, *48*, 1947
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F. Reessing, W. Szymanski, *Curr. Med. Chem.* **2017**, *24*, 4905
M. W. H. Hoorens, W. Szymanski, *Trends. Biochem. Sci, under revision*

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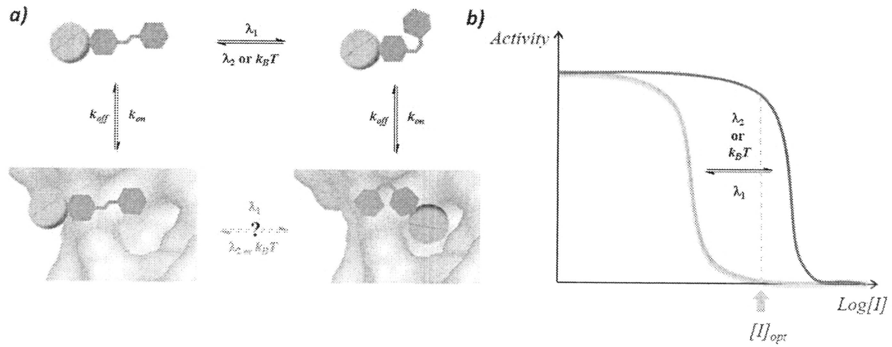

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M. W. H. Hoorens, W. Szymanski, *Trends. Biochem. Sci,* **2018**, *43*, 567

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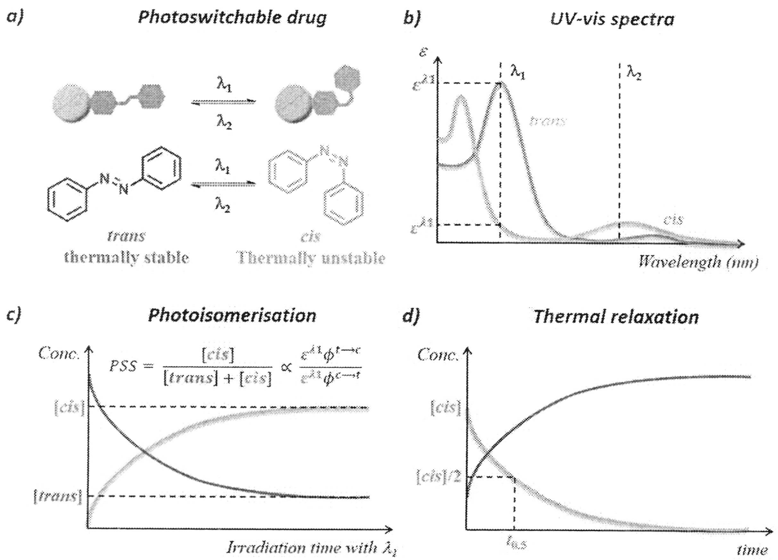
Azobenzene: the main tool



M. W. H. Hoorens, W. Szymanski, Trends. Biochem. Sci, **2018**, *43*, 567
A. A. Beharry, G. A. Woolley, *Chem. Soc. Rev.* **2011**, *40*, 4422-4437

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Photopharmacology: opportunities

Avoiding severe side-effects in chemotherapy

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- Poor drug selectivity stems from a drug's affinity for targets other than that intended.
- Cytotoxic anti-neoplastic agents are infamous for their severe side effects.

Edwards, I. R. *et al. Lancet* **2000**, *356*, 1255; Sawyers, C. L. *Nature* **2008**, *452*, 548; Reina J.A.; *Seizure*, **2014**, *23*, 184; Hassett, M. J. *et al. J. Natl. Cancer Inst.* **2006**, *98*, 1108; Ihbe-Heffinger, A. *et al. Support Care Cancer.* **2013**, *21*,1665-1675.

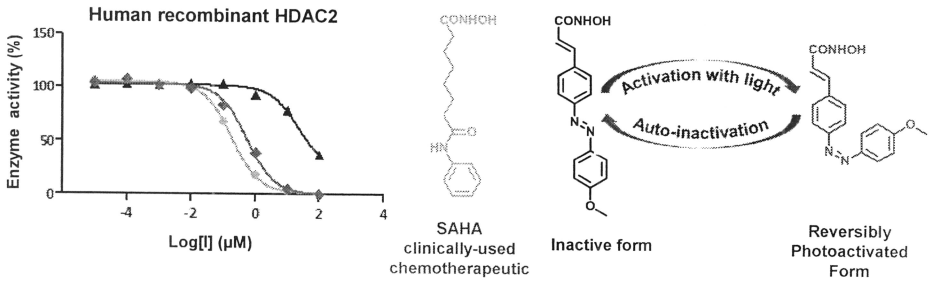
Tackling Antibiotic Resistance

- bacterial resistance stems from the build-up of antibiotics in the environment
- one of humanity's "ticking time-bombs"
- bacterial infections emerge that cannot be treated by any of the known antibiotics

Carlet, J. *et al. Lancet* **2011**, *378*, 369; Martinez, J. L. *Science* **2008**, *321*, 365; Goossens, H. *et al. Lancet* **2005**, *365*, 579; Tello, A. *et al. Environ. Health Perspect.* **2012**, *120*, 1100; Kemper, N. *Ecol. Indic.* **2008**, *8*, 1–13

Example 1: Photocontrol of HDAC Inhibition

Photopharmacological chemotherapeutics



W. Szymanski, M. E. Ourailidou, W. A. Velema, F. J. Dekker, B. L. Feringa
Chem. Eur. J. **2015**, *21*, 16517–16524

Histone decaetlases and SAHA

Histone Deacetylases (HDACs)

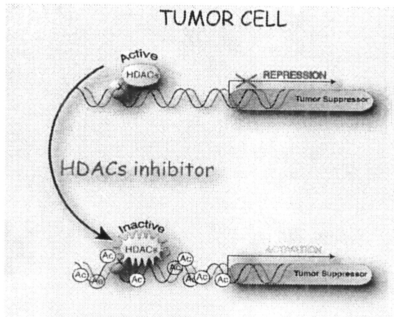
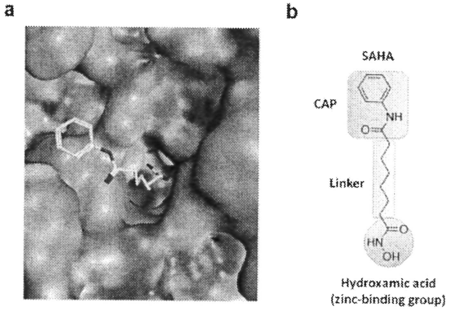


Figure 3 HDACs as targets for cancer therapy

http://www.ifom-ieo-campus.it/research/chiocca.php

HDACs deacetylate of ε-acetylated lysine residues on histone tails,
→ positive charge of the histones
→ electrostatic interactions with DNA,
→ condensed and transcriptionally silent chromatin structures.

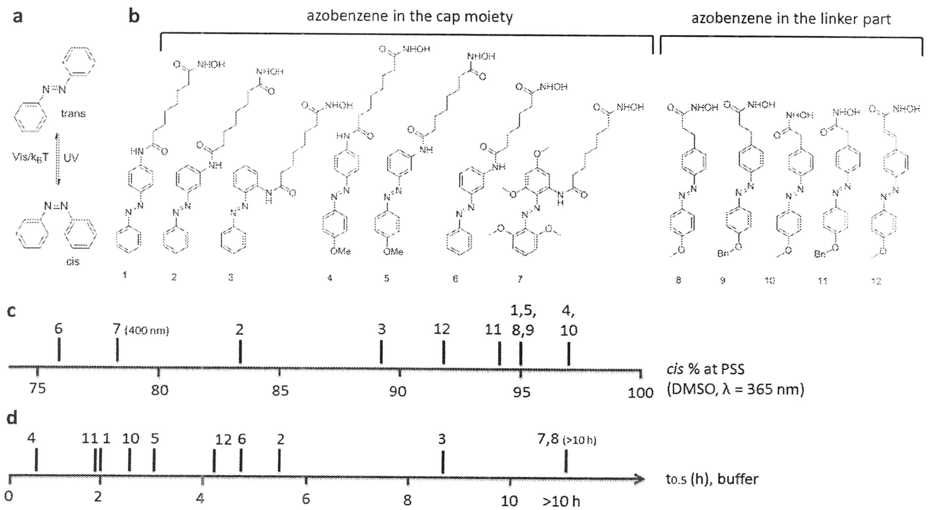
SAHA (Vorinostat)



SAHA non-selectively inhibits classes I, II and IV HDACs with a nM scale potency and is successfully applied as chemotherapeutic agents for the treatment of hematologic malignancies

O. Khan, N. B. La Thague, *Nat. Clin. Pract. Oncol.* **2008**, *5*, 714-726. P. A. Marks, R. Breslow, *Nat. Biotechnol.* **2007**, *25*, 84-90.

Molecular design & photochemical properties



W. Szymanski, M. E. Ourailidou, W. A. Velema, F. J. Dekker, B. L. Feringa
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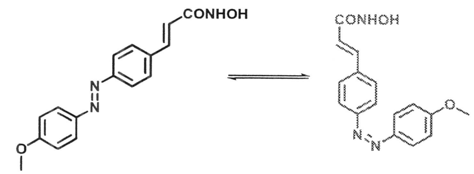
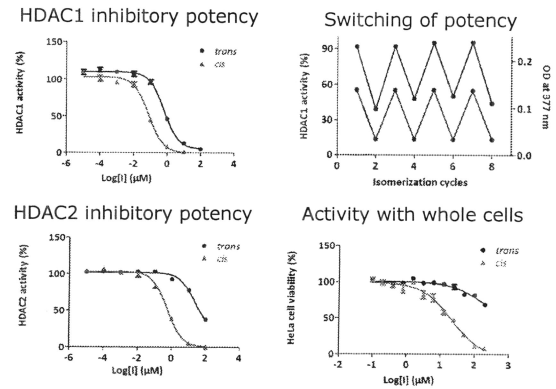
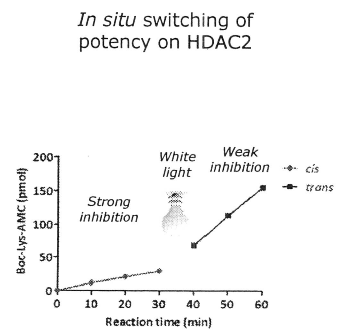
Properties of the best design



PSS at λ = 365 nm: 92% (DMSO)

Half-life at 37 °C in cell buffer: 67 min





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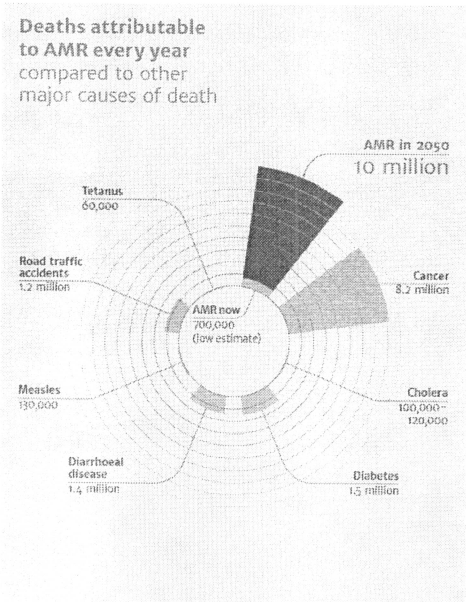
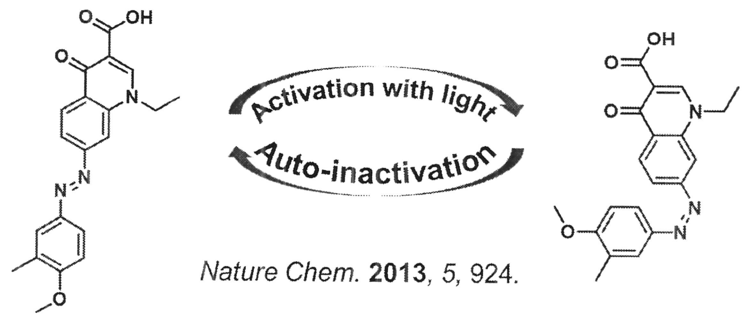
Photocontrol of antimicrobial activity



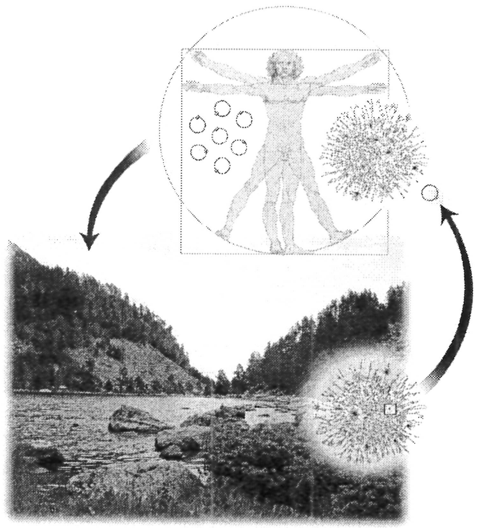
Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. 2014

Photocontrol of antimicrobial activity



Nature Chem. **2013**, *5*, 924.

Antibiotics in environment



The quinolone resistance gene *qnr* is present in the chromosomes of waterborne bacteria (unknown function).

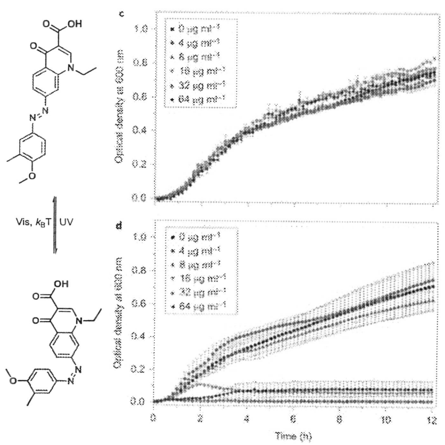
After being integrated in plasmids, where it is constitutively expressed, *qnr* contributes to low-level resistance of its new bacterial host to quinolones.

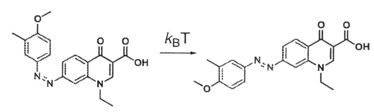
Contamination of river waters by quinolones enriches for plasmid-encoded *qnr* genes present in waterborne bacteria, in such a way that may allow a first step in the transfer of this gene to human pathogens.

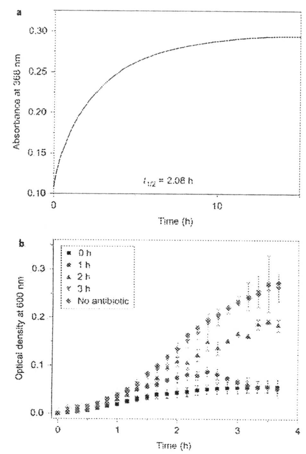
Emerg Infect Dis. 2008 Feb; 14(2): 231–237.
Science 2008 Vol. 321 pp. 365-367.

Photocontrol of antimicrobial activity

Difference in activity between the photoisomers

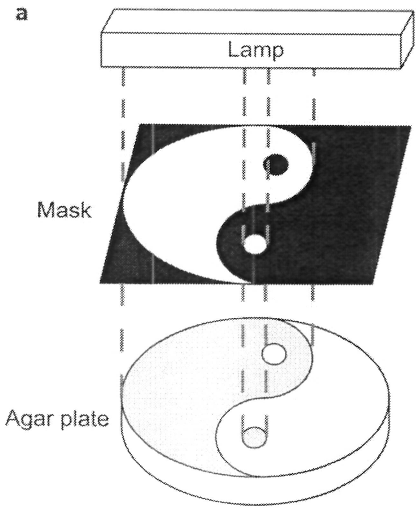






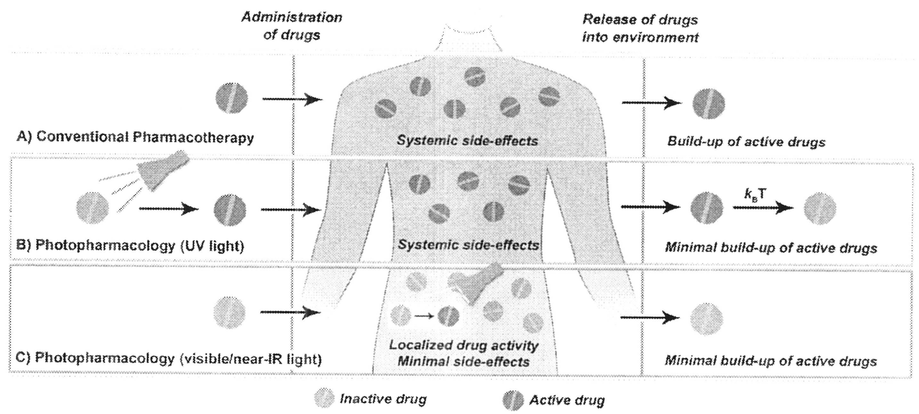
Nature Chem. **2013**, *5*, 924.

Photocontrol of antimicrobial activity



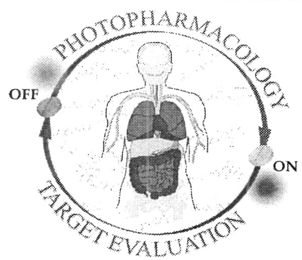
Nature Chem. **2013**, *5*, 924.

Photocontrol of antimicrobial activity *in vivo*

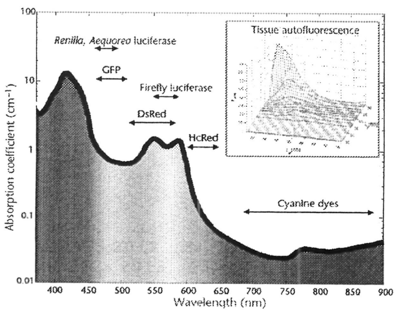


M. Wegener, M. J. Hansen, A. J. M. Driessen, W. Szymanski, B. L. Feringa *JACS,* **2017**, *139*, 17979–17986

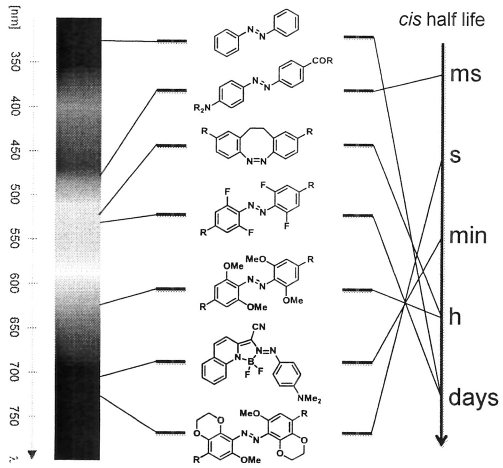
A Challenge : visible light



Angew. Chem. Int. Ed. **2016,** 10978

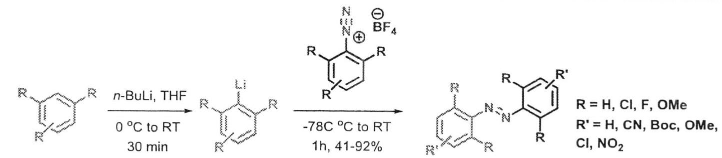


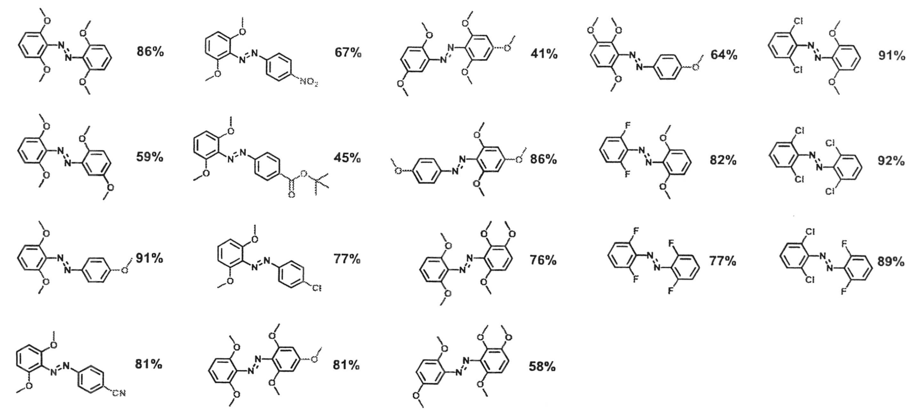
Weissleder, R.; Ntziachristos , V.
Nat. Medicine. **2003**, *9, 123.*



Siewertsen, R. *et al. JACS.* **2009**, *131*, 15594
Bleger, D. *et al. JACS* **2012**, *134*, 20597
Samanta, S. *et al. JACS* **2013**, *135*, 9777
Yang, Y. *et al. JACS* **2014**, *136*, 13190
Dong, M. *et al. JACS* **2017**, *139, 13483*

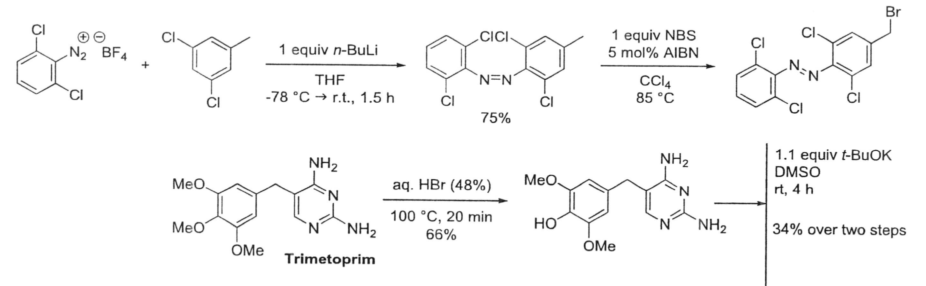
Visible light switches

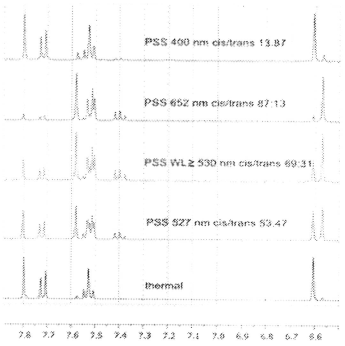


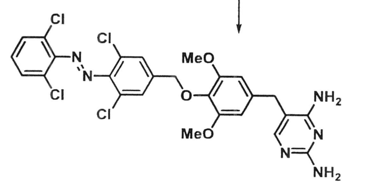


Mickel J. Hansen, Michael M. Lerch, Wiktor, Szymanski, Ben L. Feringa
Angew. Chem. Int. Ed. **2016,** *55*, 13514–13518

Photocontrol of antimicrobial activity







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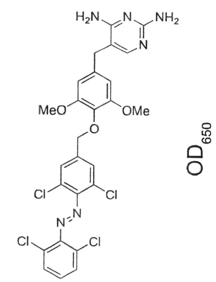
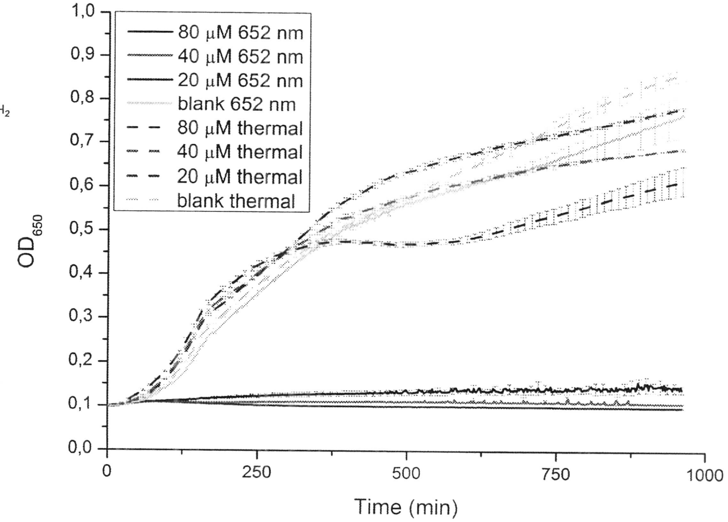
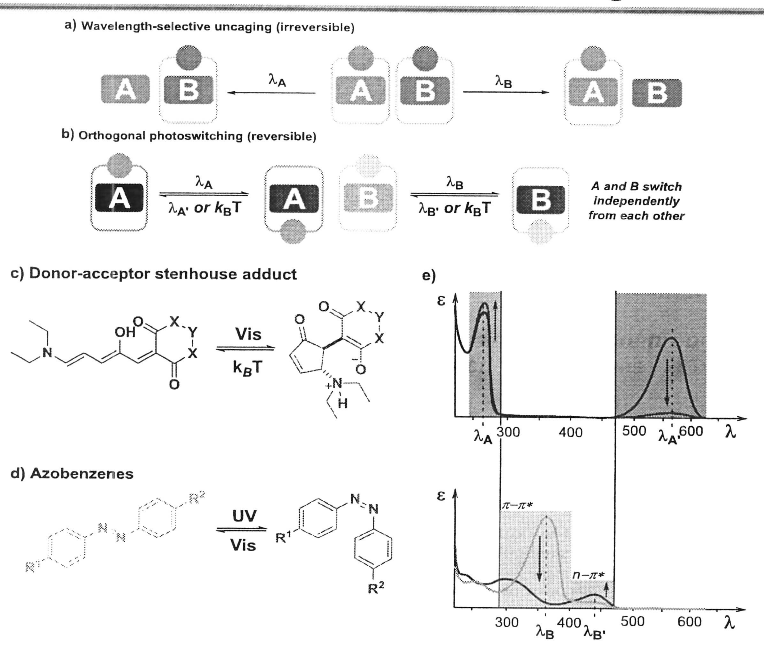


Pre-irradiation in DMSO



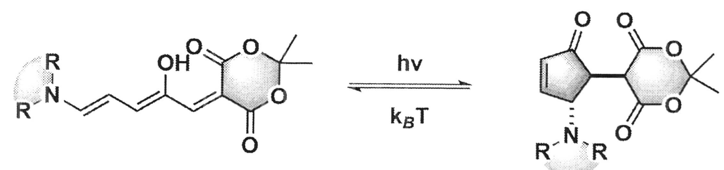
M. Wegener, M. J. Hansen, A. J. M. Driessen, W. Szymanski, B. L. Feringa
JACS, **2017**, *139*, 17979–17986

Outlook: orthogonal switching



Donor-Acceptor Stenhouse Adducts

Stenhouse Switches



- *Explaining* ***structure-properties relationships*** *and* ***photoswitching mechanism***
- ***Practical guidelines***

General review on DASAs:
M. M. Lerch, W. Szymanski, B. L. Feringa, Chem. Soc. Rev. **2018,** 47, 1910

For the invention of DASA, see:
Hawker, Read de Alaniz anc co-workers, *J. Am. Chem. Soc.* **2014**, *136,* 8169

DASA switching mechanism:
M. M. Lerch, S. J. Wezenberg, W. Szymanski, B. L. Feringa *J. Am. Chem. Soc.* **2016**, *138*, 6344
M. Di Donato, M. M. Lerch *et al. J. Am. Chem. Soc* **2017**, *139*, 15596
M. M. Lerch, M. Medved *et al. J. Phys. Chem. A* **2018**, *122*, 955

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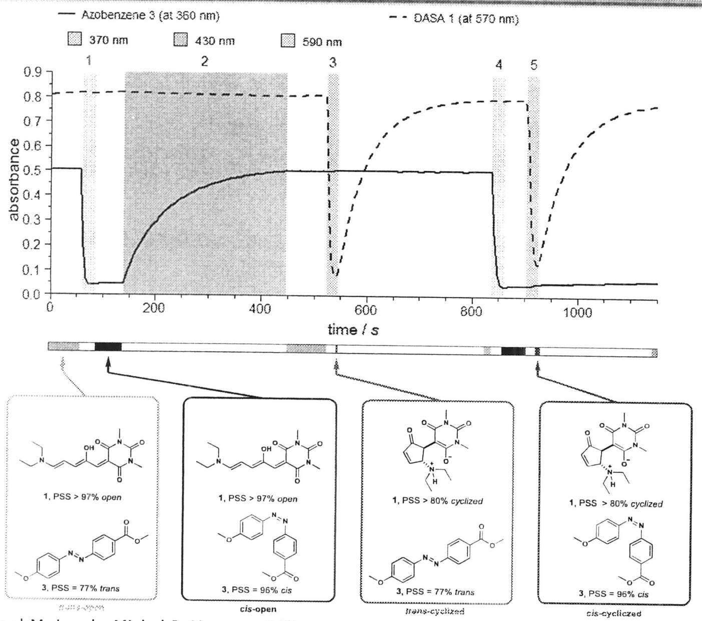

Michael M. Lerch, Mickel J. Hansen, Willem. A. Velema, Wiktor Szymanski, Ben L. Feringa, *Nature Communications* **2016**, 7, 12054

Acknowledgments

University of Groningen:
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Dr. Lucien Lameijer
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Dr. Claudia Poloni
Friederike Reessing
Kaja Sitkowska
Laura Slappendel
Dr. Wim Velema
Jana Volaric
Dr. Michael Wegener
Ilse Welleman

Prof. Arnold Driessen
Prof. Frank Dekker
Dr. Maria Eleni Ourailidou
Dr. Jan Pieter Van der Berg

University Medical Center Groningen:
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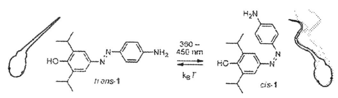
www.szymanski-lab.com

www.photopharmacology.nl

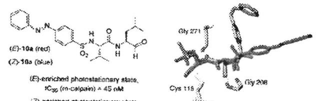
International Symposium on Photopharmacology, Groningen 2017

Neuronal signaling



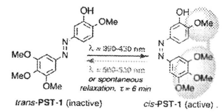
Trauner, Gorostiza, Llebaria, Wanner, Kramer, Isacoff...

Hydrolase inhibitors



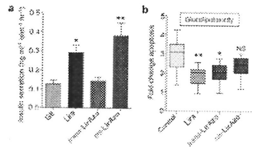
Abell, Decker, Sterner, König, Uchida...

Photostatins



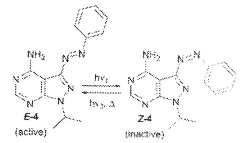
Thorn-Seshold, Trauner, Streu, Hartman

Insulin secretion



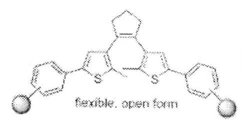
Trauner, Hodson

Kinase inhibitors



Andréasson, Grøtli, Peifer, König

Anti-Tuberculosis agents



Branda, König