MUNI PHARM

Department of Natural Drugs

Supramolecular Pharmacy

12. Photopharmacology

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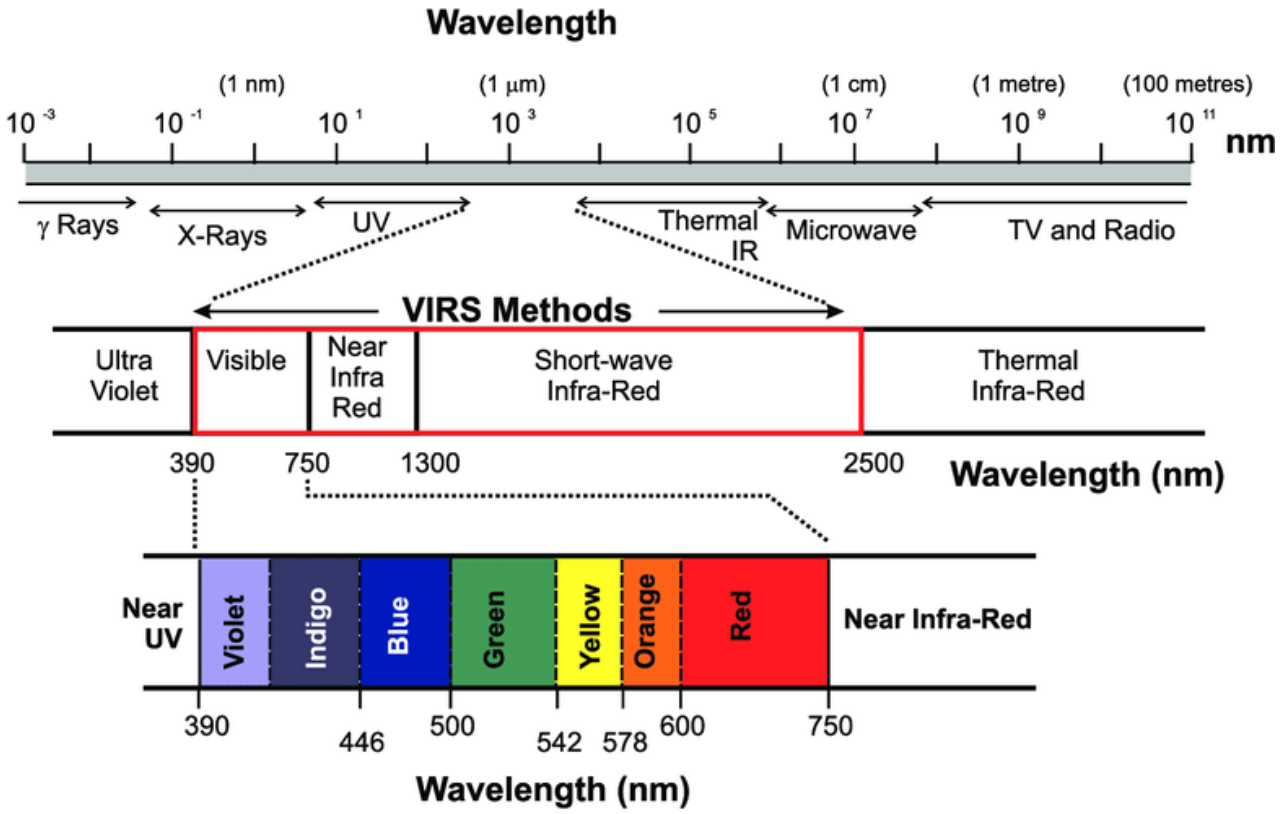
Photopharmacology

- Emerging approach in medicine using activation and deactivation of photoswitchable molecules with light for targeted drug delivery
- Photopharmacology refers to bioactive molecular systems that undergo reversible photochemical transformation that alter their pharmacokinetics and pharmacodynamics
- Allows to achieve control of when and where drugs are active in a reversible manner and to prevent side effects
- Switching drugs "on" and "off" is achieved by introducing photoswitches such as azobenzene, spiropyran, diarylethene, anthracene, or stilbene into a drug
- Photomediated reactive oxygen generation, small molecule activation, micelle, nanoparticle disruption, and material degradation (e.g., gels) are the most common

Spectral range

- Light is uniquely powerful tool for controlling molecular events in biology
- No other external input (*e.g.*, heat, ultrasound, magnetic field) can be so tightly focused or so highly regulated as a clinical laser



DeForest et al. *Adv. Drug Del. Rev.* 2021, *171*, 94–107.

Light sources

- **Mercury Arc lamps** (250-600 nm) broad-spectrum of light which can be refined to desired wavelengths with bandpass filters (typically 254, 365, 405, 436, 546, and 579 nm) – relatively cheap and high power

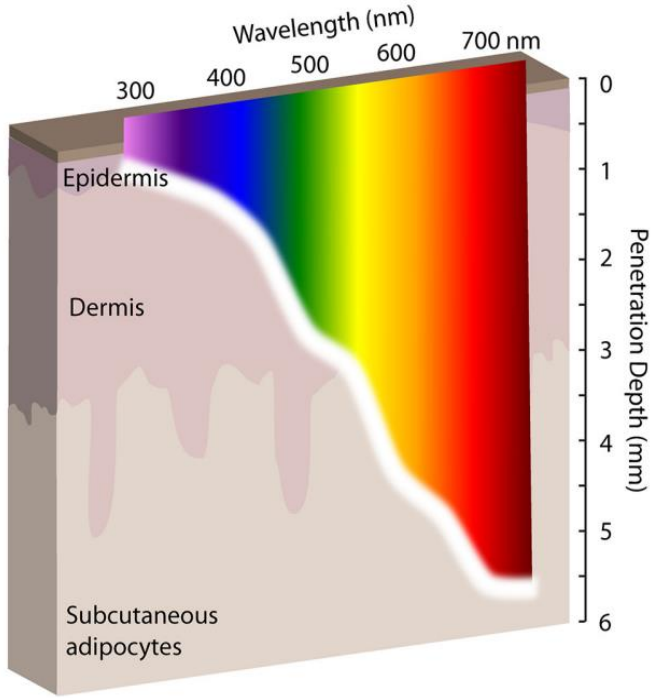
- **LEDs** (250-700 nm) wide variety of wavelengths and intensities – the full-width half maximum value might extend ± 10-20 nm beyond the reported wavelength

- **Lasers** (250-900 nm) have highly focused beam and narrow bandwidth (centered to ±1 nm), laser pointers cannot readily change intensity

DeForest et al. *Adv. Drug Del. Rev.* 2021, *171*, 94–107.

Challenges of photopharmacology

- X-rays or radio waves may pass through the body with relative ease, visible, UV, and infrared (IR) light experience variable and high levels of absorption/scattering by living tissue
- Poor penetration depth of low-energy electromagnetic radiation
- The greatest depth of penetration is achieved by low-energy IR light, with 750 nm light penetrating ~5 mm below the skin's surface
- High amounts of light scattering as well as high absorption of hemoglobin and melanin
- Selectively using different wavelengths of light allows researchers to potentially trigger multiple events separately and/or sequentially
- Facile control over the intensity and wavelength of the light could allow dosing of the active drug



DeForest et al. *Adv. Drug Del. Rev.* 2021, *171*, 94–107.

Properties of photoactive molecules (photoswitches)

- Molar absorptivity = refers to capacity of compound to absorb light of a specific wavelength
- Excitation wavelengths
- Quantum yield = the ratio of the number of photons emitted to the number of photons absorbed (describes how efficiently a fluorophore converts the excitation light into fluorescence)
- Photostationary state = equilibrium chemical composition under a specific kind of electromagnetic irradiation
- Stability (thermo-, solvato-, acido-, mechano-)

Challenges of photopharmacology

- The most effectively penetrating wavelengths are in the visible-IR regions, generally accepted to be between 650–900 nm (near-infrared phototherapeutic window) (λ<650 nm – absorption by hemoglobin, λ>900 nm water)

- The most organic and inorganic chromophores have molar absorptivities (10^4–10^5 M^{-1} cm^{-1} at 500 nm) that exceed those of biological chromophores such as human rhodopsin in the eye (~10^4 M^{-1} cm^{-1} at 500 nm), the comparatively high concentration of the latter can necessitate fairly large light dosages to phototrigger engineered material changes

- Since quantum yields are often lower than desired for many traditional photochemical reactions, the flux of light required may near the range of thermal tissue damage, especially in the use of high-energy light

DeForest et al. *Adv. Drug Del. Rev.* 2021, *171*, 94–107.

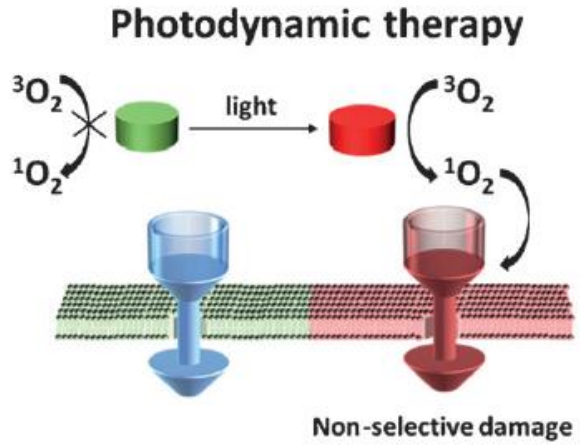
Photopharmacology

1. Photodynamic therapy
2. Optogenetics
3. Photopharmacology

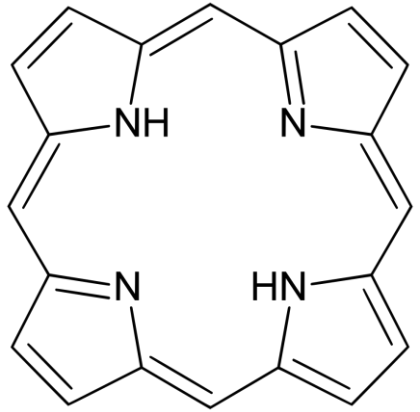
Feringa et al. *Angew. Chem. Int. Ed.* 2016, 55, 10978–10999.

1. Photodynamic therapy (PDT)

- Uses dyes that relax from their light-induced excited state by converting available triplet oxygen ($^3O_2$) into highly toxic singlet oxygen ($^1O_2$) (reactive oxygen species – ROS) – tissue ablation
- Singlet oxygen is short-lived, its toxicity can be contained in a small volume, thereby leading to spatial selectivity of the therapy
- Several PDT drugs are in clinical trials and some underwent FDA approval
- This goes hand in hand with innovations in light application devices in the clinic, enabling light to be delivered to any region in the body with varying levels of invasiveness



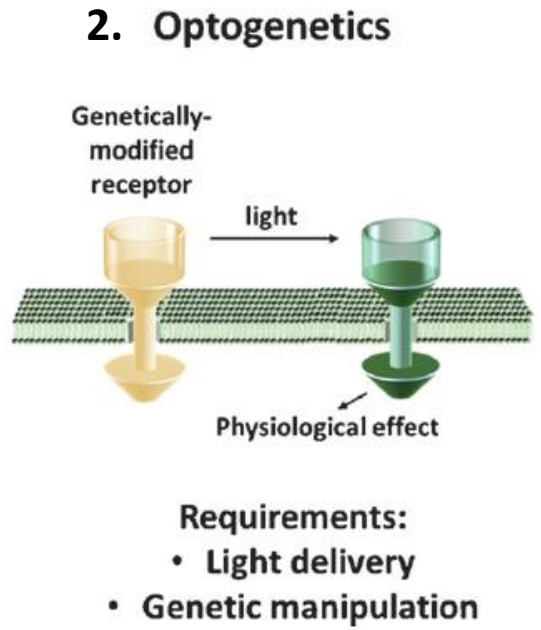
Requirements:
- **Light delivery**
- **Presence of oxygen**



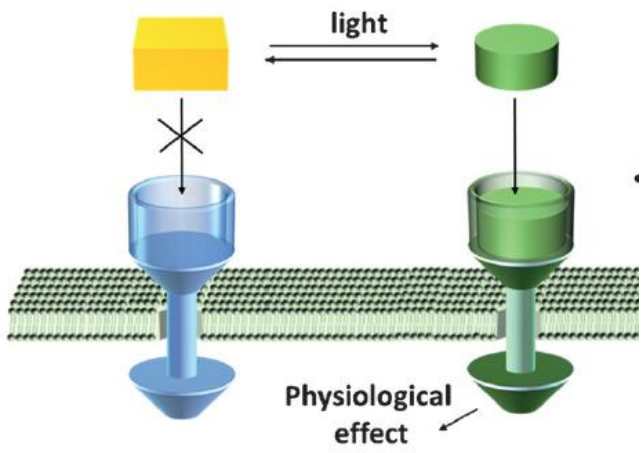
DeForest et al. *Adv. Drug Del. Rev.* 2021, *171*, 94–107.

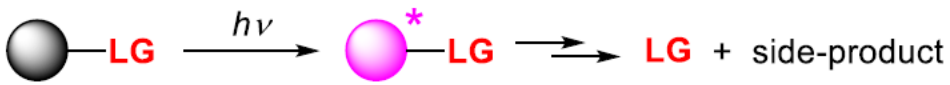
2. Optogenetics

- Biological technique to control the activity of neurons and other cell types with light
- Achieved by expression of light-sensitive ion channels, pumps or enzymes in target cells
- Using the optogenetic technology scientist could map functional connectivity of the brain as well as to understand neural contribution to decision making, learning, fear memory, addiction, locomotion, etc.
- It led to first medical application where vision was restored to a blind patient

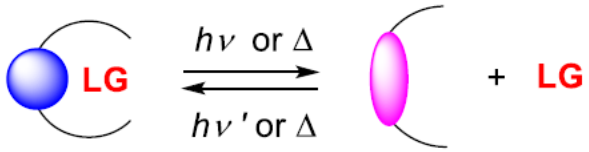


3. Photopharmacology

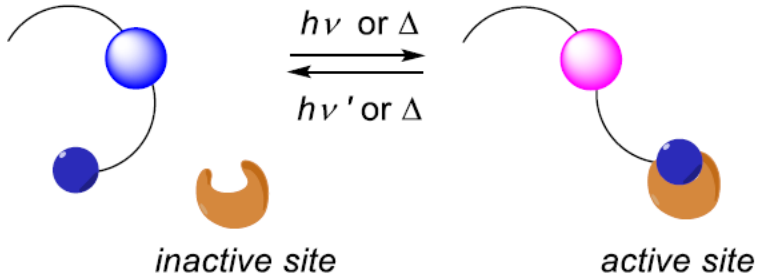




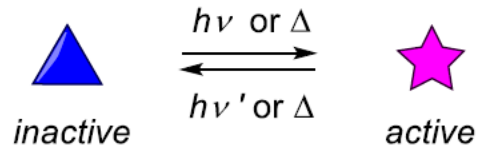
(a) irreversible release (uncaging)



(b) photoswitchable carrier (an active species is released)



(c) photoswitchable tether (an active species is tethered)



(d) reversible activation and inactivation of a substrate

Klán et al. *Chem. Rev.* 2020, 120, 13135-13272.

3. Photopharmacology

Circulating drug carriers: small-molecule prodrugs, micelles, and liposomes

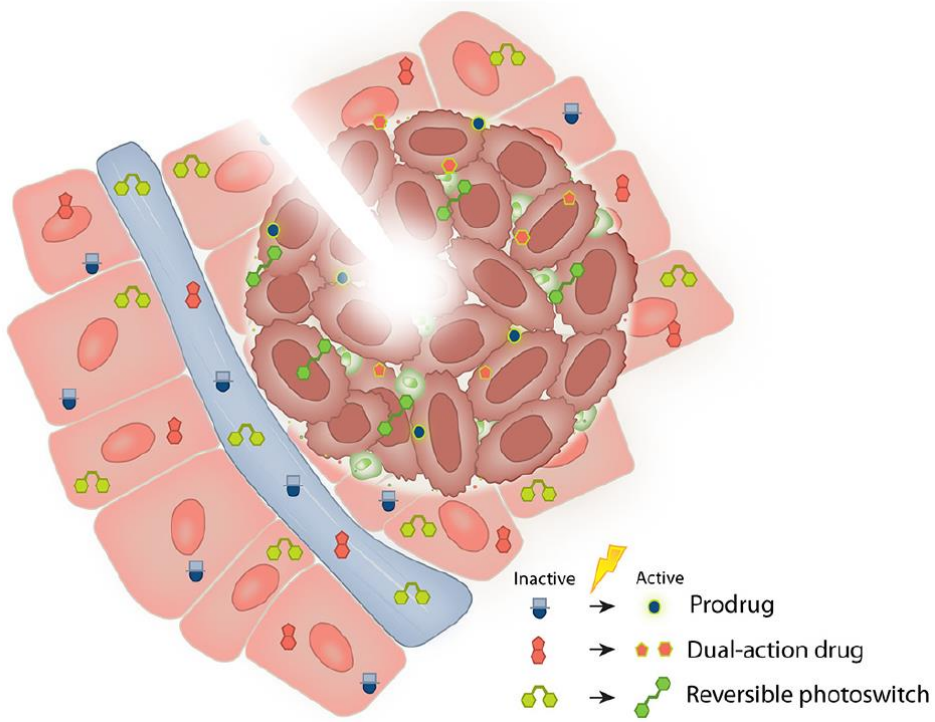
- Small molecule prodrugs
  - Photocaged small molecules for *in vitro* discovery
  - Caged prodrugs for targeted delivery
    - Transition-metal complexes as photocages and dual-action prodrugs
    - Small-molecule light-activated theranostic approaches
    - Photoregulating gene expression
- Nanoparticle delivery vehicles: micelles, liposomes, and nanoparticles
  - Disrupting nanostructures with organic photosensitizers
  - Disrupting nanostructures with inorganic photosensitizers

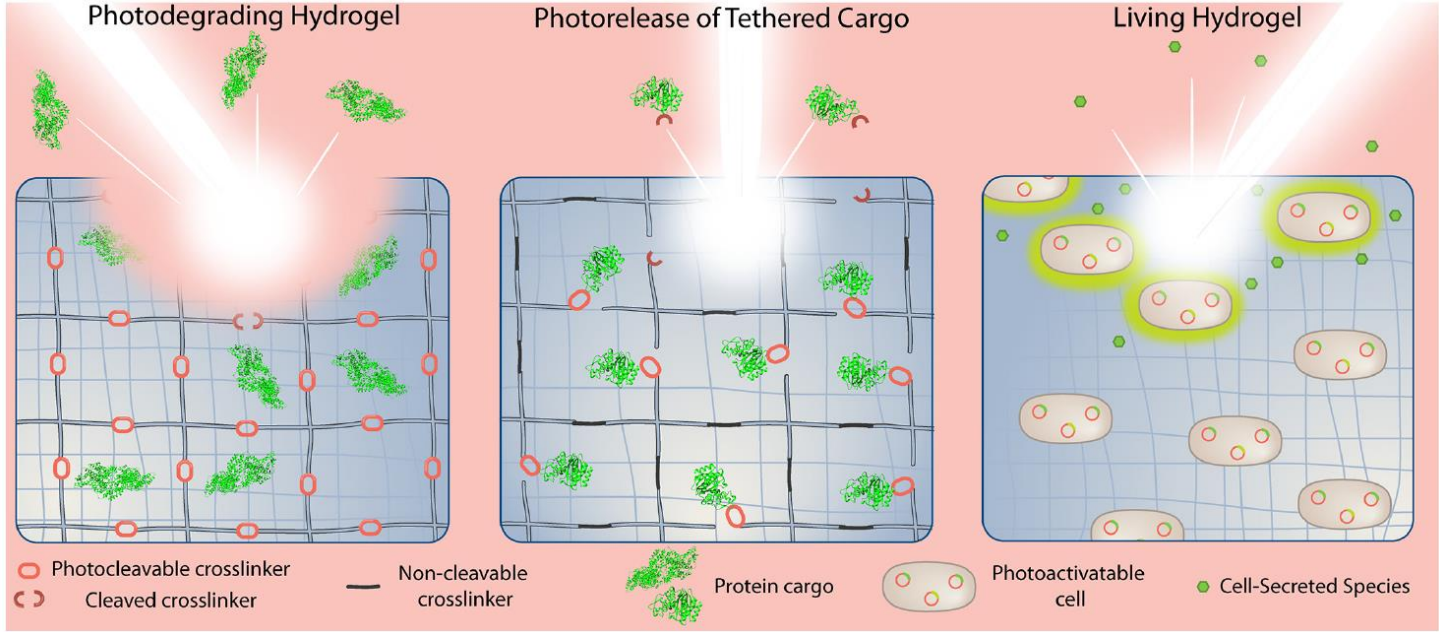
Drug-loaded depots: soft biomaterials as drug delivery platforms

- Phototriggered drug release from hydrogels
  - Photodegradable hydrogels for drug delivery
  - Photocleavable linkers to release tethered cargo
- Directing cell growth *in vitro* with light
- Light-responsive living hydrogels

DeForest et al. *Adv. Drug Del. Rev.* 2021, *171*, 94–107.

Photopharmacology selected mechanisms



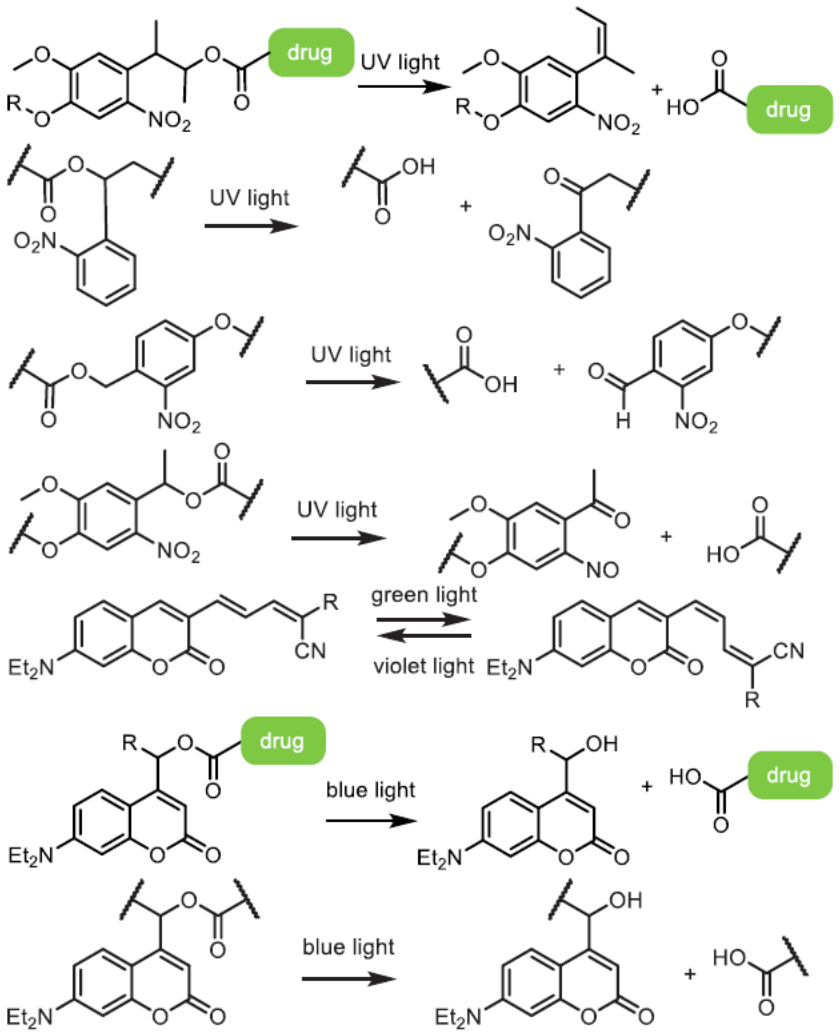


DeForest et al. *Adv. Drug Del. Rev.* 2021, *171*, 94–107.

Photocleavable groups

Ortho-nitrobenzyl

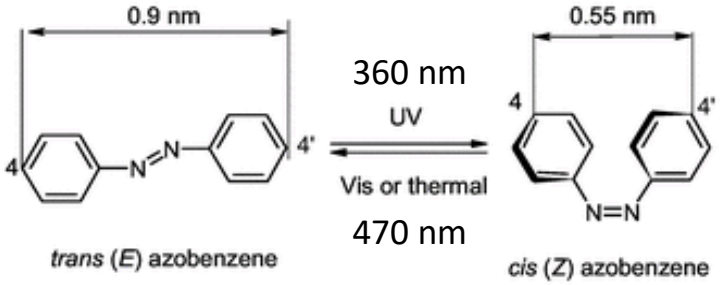
Coumarin



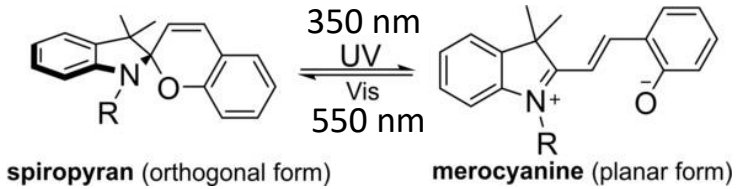
a) DeForest et al. *Adv. Drug Del. Rev.* 2021, *171*, 94–107, b) Klán et al. *Chem. Rev.* 2020, 120, 13135-13272.

Molecular photoswitches

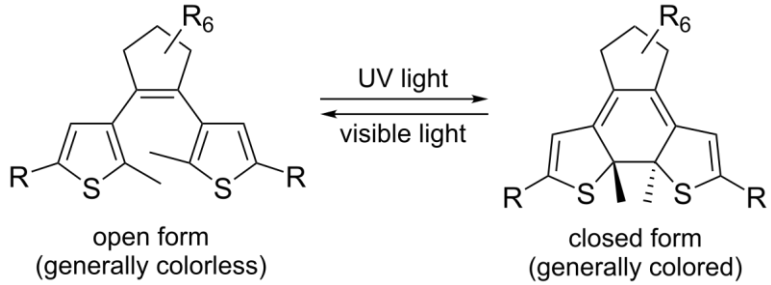
Azobenzen switches



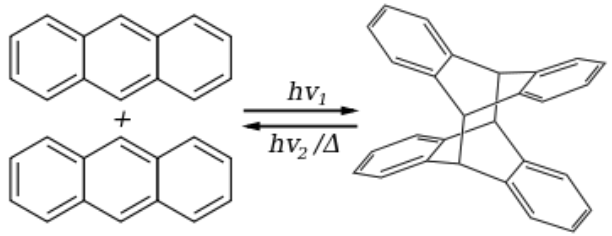
Spiropyrans



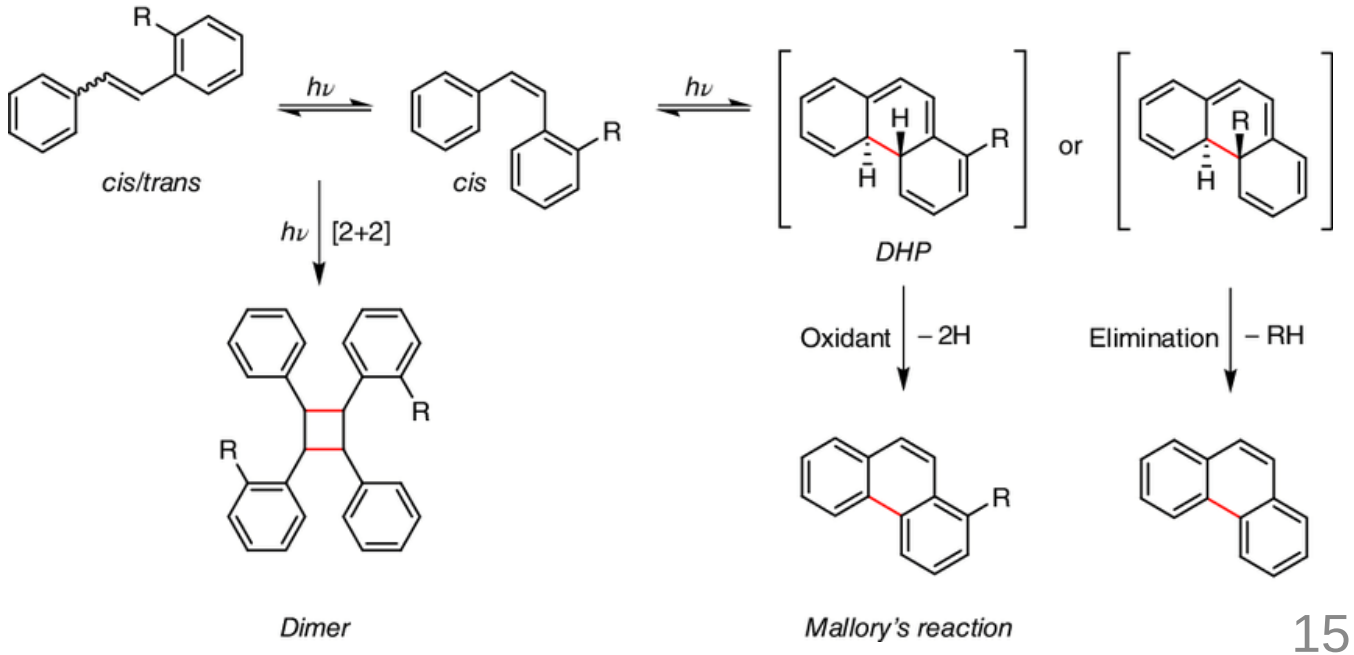
Dithienylethenes



Anthracenes

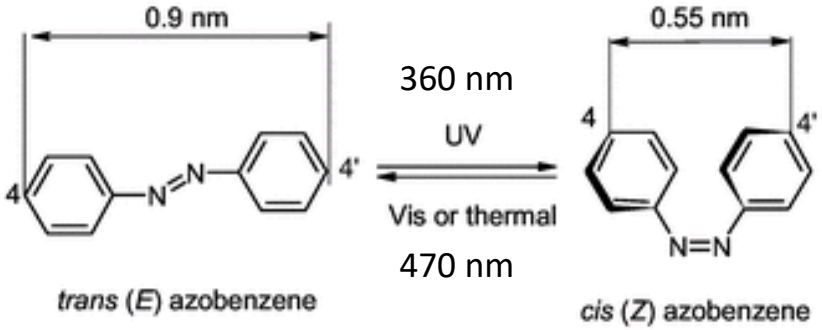


Stilbenes



Molecular photoswitches

- ***Azobenzene photoswitches***

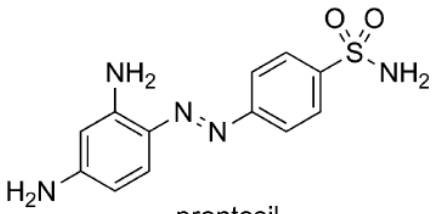


  - the most common used photoswitches (simple synthesis, photostability, reliability)
  - the planar *E* isomer goes into bulkier *Z* isomer
  - azobenzenes show high quantum yields for both *Z/E* and *E/Z* photoisomerizations, and high photostationary state ratios
  - nearly all the photophysical and photochemical properties of azobenzenes, in particular quantum yield, thermal stability of Z-isomer, photostationary state ratios, excitation wavelengths, can be tuned easily by introducing appropriate substituents at the azobenzene core
  - well-described in literature

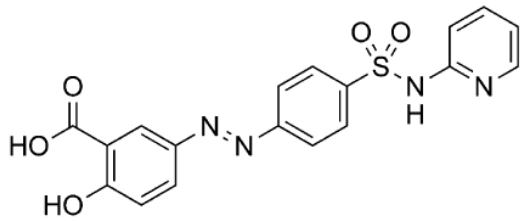
Feringa et al. *Nanoscale Adv.* 2021, *3*, 24–40.

Molecular photoswitches

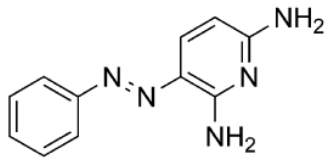
- ***Azobenzene photoswitches***



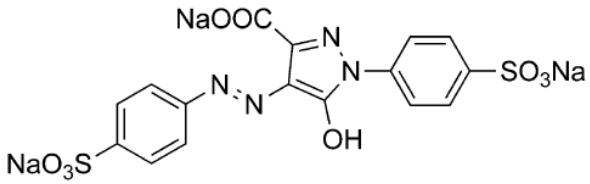
prontosil



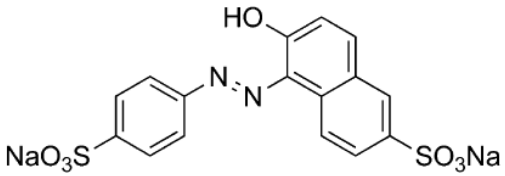
sulfasalazine



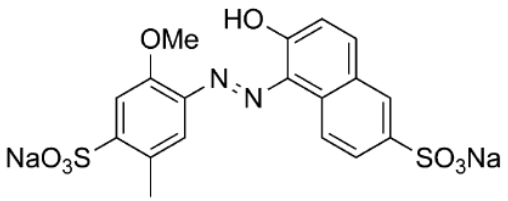
phenazopyridine



tartrazine (E102)



sunset yellow FCF (E110)

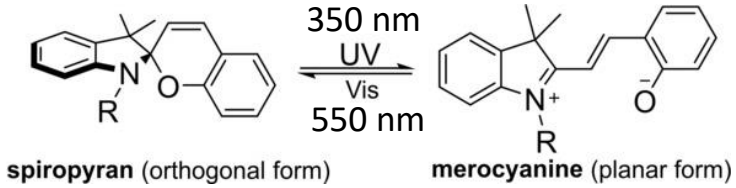


allura red AC (E129)

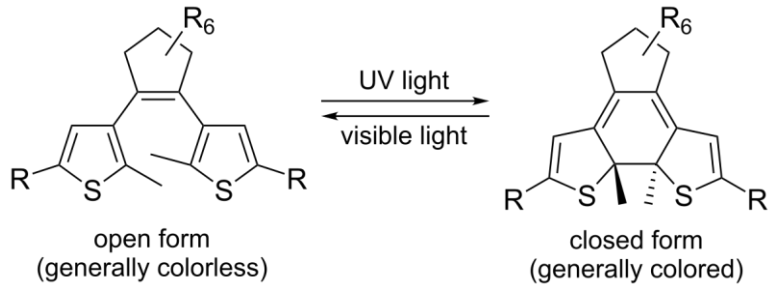
Feringa et al. *Nanoscale Adv.* 2021, *3*, 24–40.

Molecular photoswitches

- ***Spiropyrans***
  - Colorless spiropyrans undergo UV light induced isomerization to the zwitterionic, colored merocyanine form
  - Spiropyran form can be regenerated by irradiation at longer wavelengths or by heating and the transoid merocyanine form can be stabilized by protonation
  - Compounds are photo- and often thermo-, acido-, solvato-, and mechano-chromic



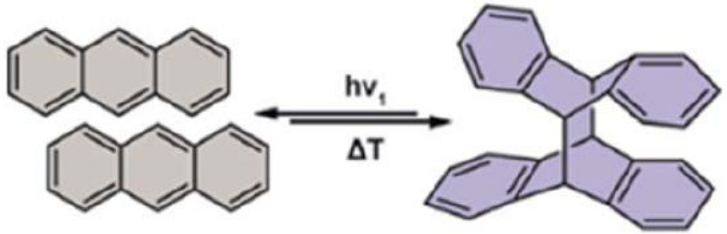
- ***Dithienylethens (DTEs)***
  - ring-opened isomer (colorless) under UV-light leads to colored, ring-closed, isomer
  - some derivatives show half-lives at RT reaching 400 000 years and a remarkably high photostability even over 10 000 isomerization cycles



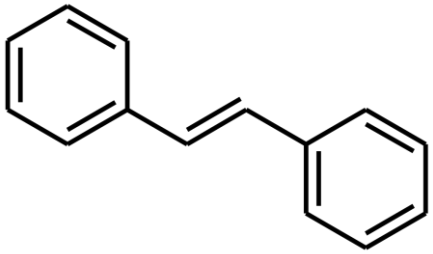
Feringa et al. *Nanoscale Adv.* 2021, *3*, 24–40.

Molecular photoswitches

- ***Anthracenes***
  - Undergo a formal [4 + 4] photocycloaddition dimerization upon exposure to UV light, while the monomerization of the photodimer can be achieved thermally
  - Requires proper stacking (intermolecular distance between reactive carbons <4.5 Å)

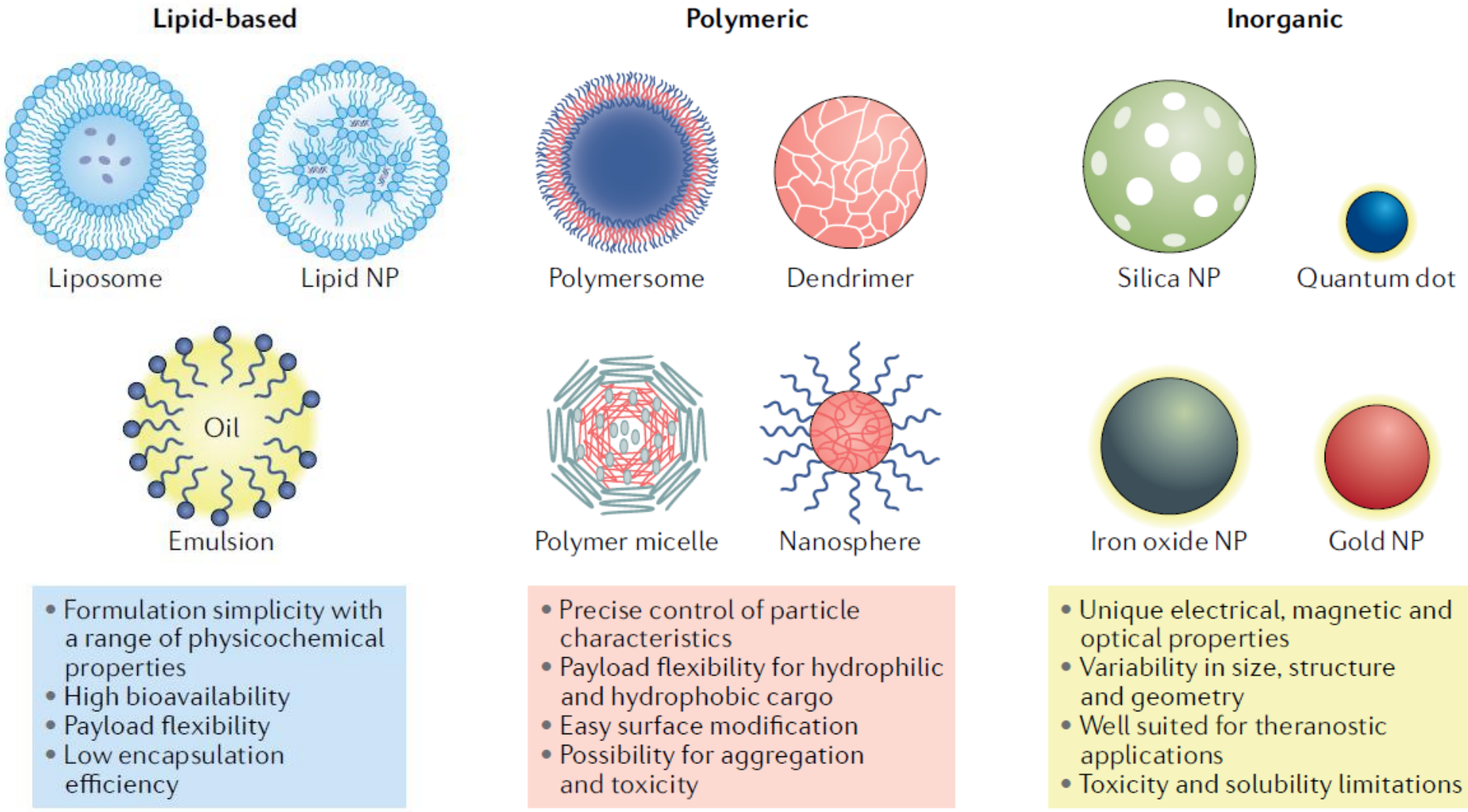


- ***Stilbenes***
  - Substitution patterns around the olefinic bond in these compounds precludes the competitive photodegradation pathways characteristic for stilbene derivatives and controls the rate of the rotary motion, thus providing a possibility to fine-tune the rate of rotation by synthetic modification



Feringa et al. *Nanoscale Adv.* 2021, *3*, 24–40.

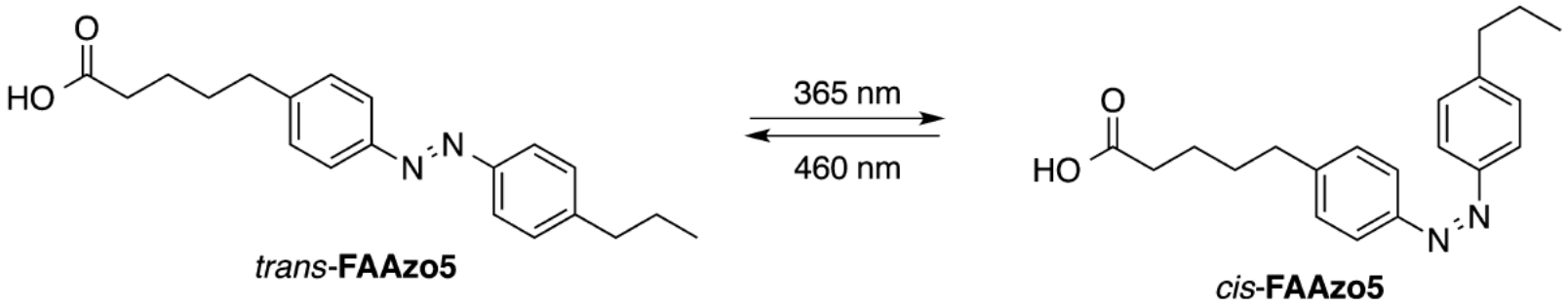
Nanoparticles in pharmacy



Mitchell et al. *Nature Reviews: Drug Discovery* 2021, 20, 101–124.

Photoswitchable lipids and amphiphiles

- Effect on the biophysical properties of a biological membrane, such as fluidity, curvature, raft formation, impedance, and capacitance
- Photolipids can operate at the interface of the lipid bilayer and a membrane protein (surrounding membrane is known to have a large influence on the dynamics of transmembrane proteins)
- Can function as more conventional ligands that bind deeply within a protein or at the protein−cytosol interface (transmembrane, membrane-associated, and cytosolic proteins, such as TRP channels, protein kinase C, or nuclear hormone receptors)



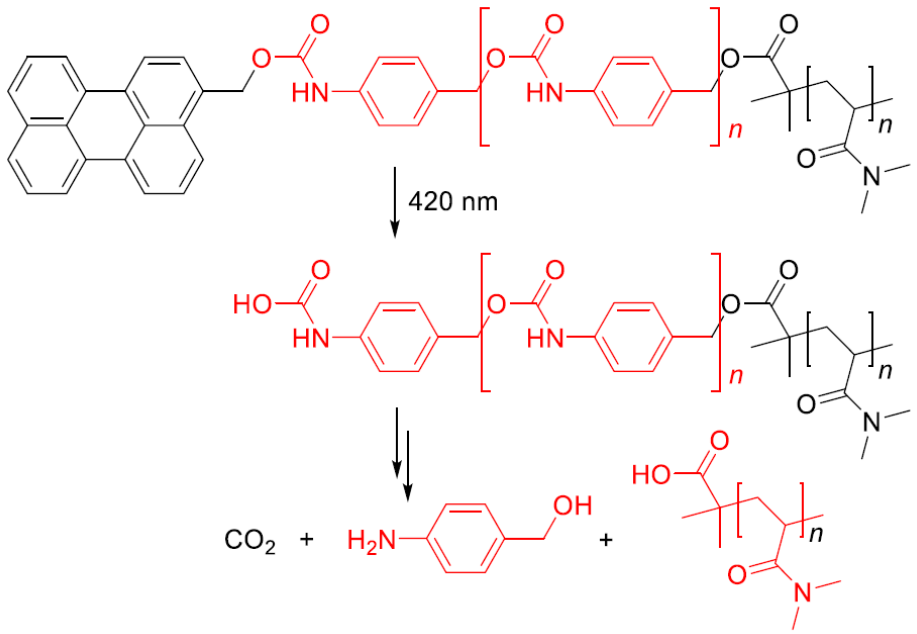
trans-**FAAzo5** *cis*-**FAAzo5**

Trauner et al. *Acc. Chem. Res.* 2015, 48, 1947−1960

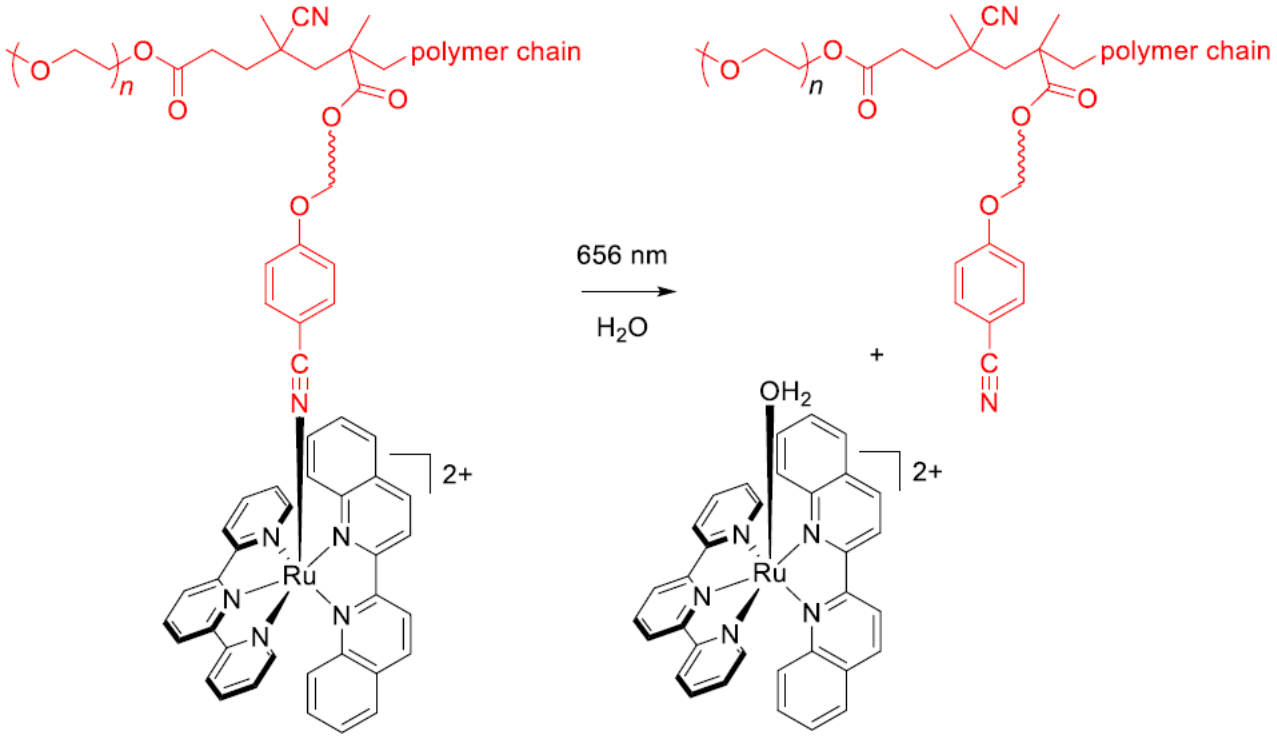
Photoswitchable polymers, micelles, and vesicles

Polymersome – photosolvolysis

- Cleavage of perylene-3-yl protecting group



Polymer NPs releasing anticancer Ru(II)

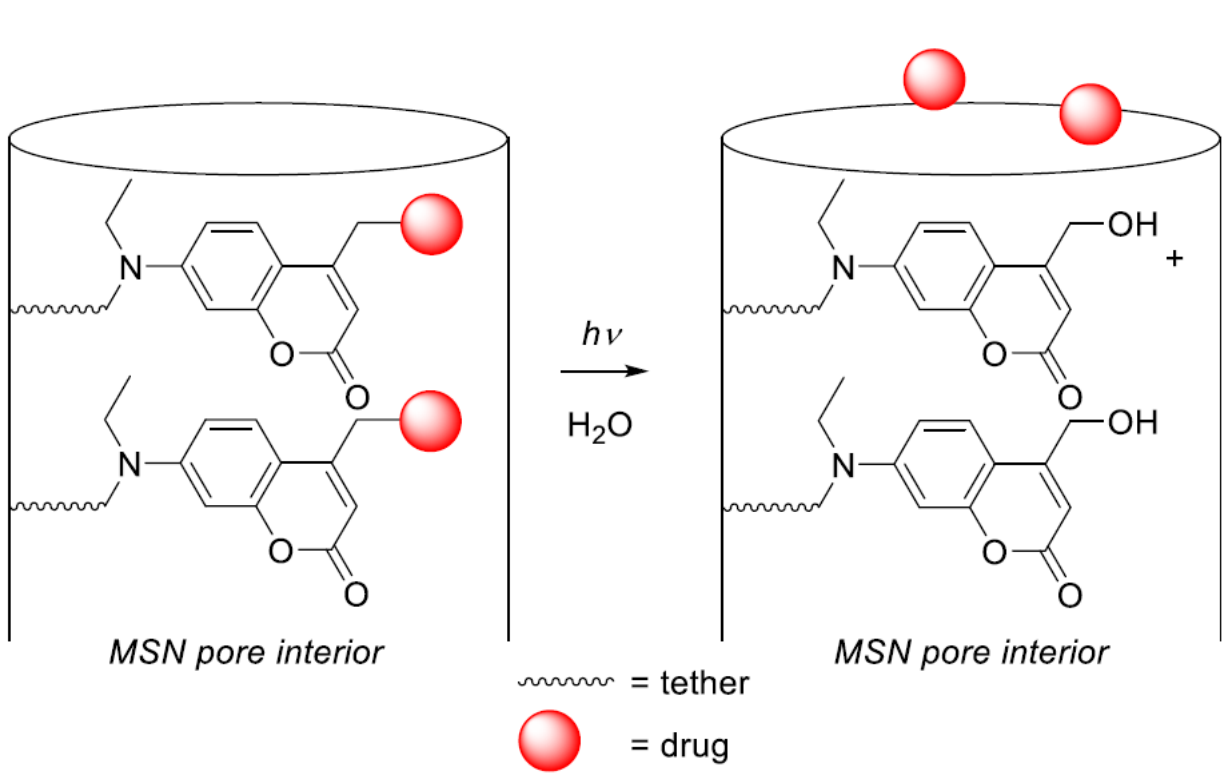


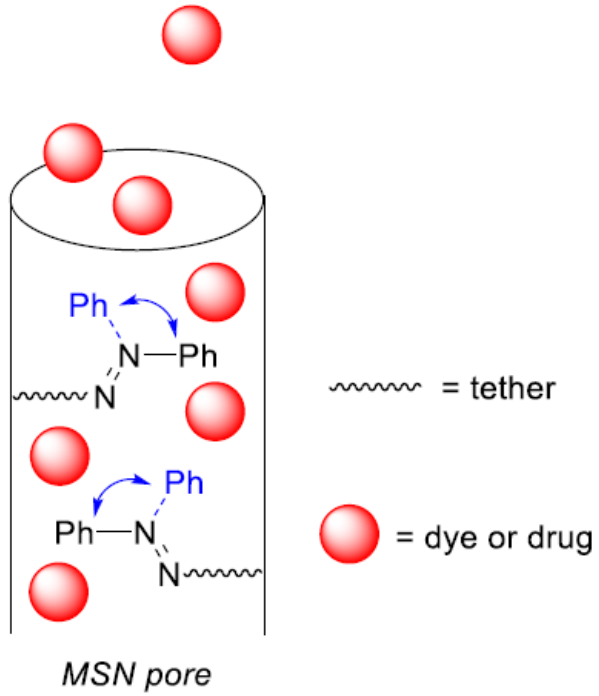
Klán et al. *Chem. Rev.* 2020, 120, 13135-13272.

Photoswitchable polymers, micelles, and vesicles

Mesoporous silica nanoparticles (MSNs)

- 420 or 800 nm light was used to release chlorambucil from 7-amino-coumarin derivative grafted onto surface of MSN

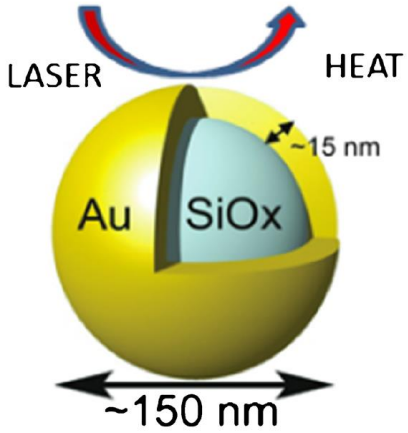


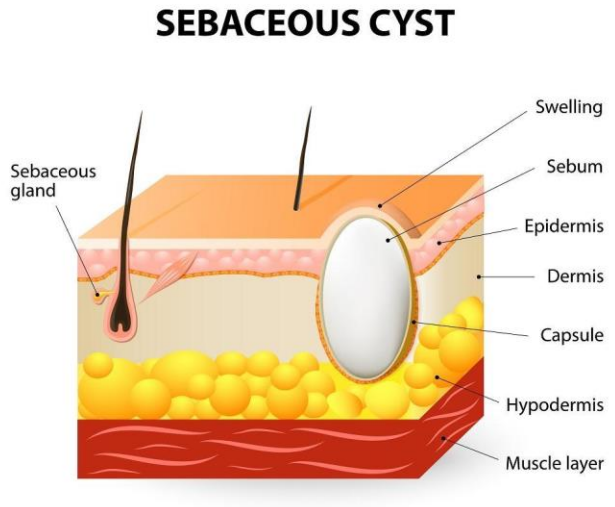


Klán et al. *Chem. Rev.* 2020, 120, 13135-13272.

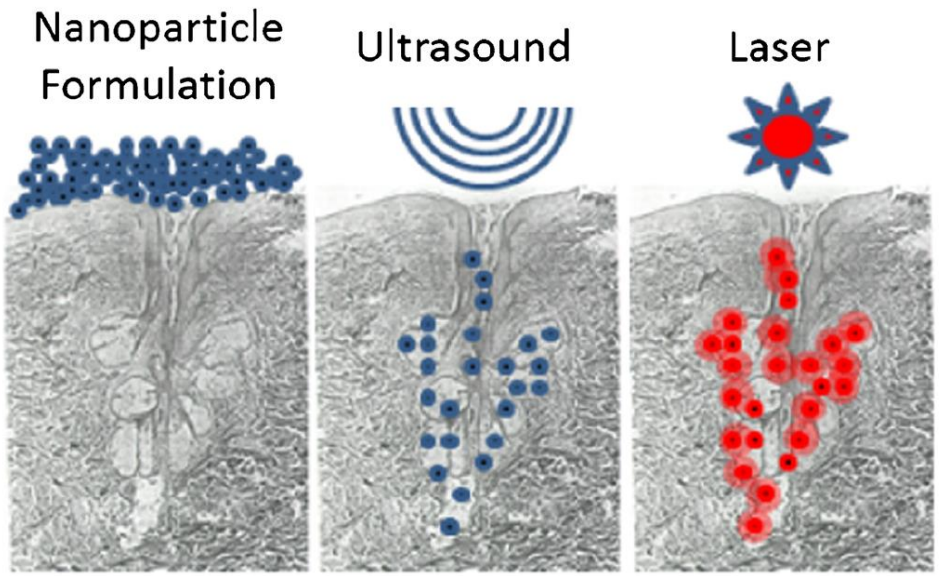
Gold nanoparticles as drugs

- AuroLase® is being developed by Nanospectra, are silica-gold nanoshells coated with (poly)ethylene glycol (PEG) designed to thermally ablate solid tumors following stimulation with a near-infrared energy source





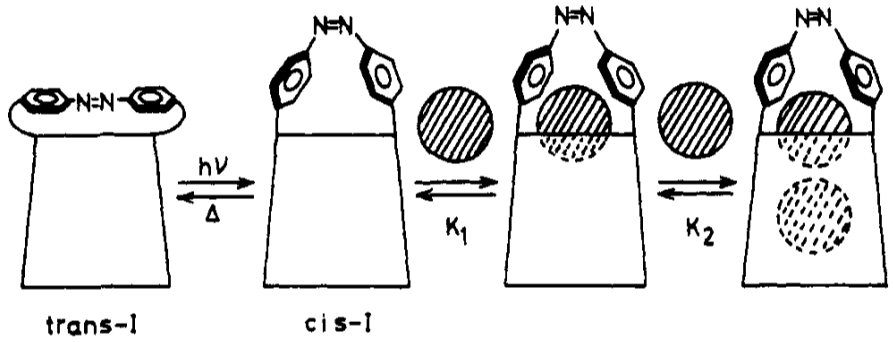
- AuNPs capable of treating acne (Sebashells) are being developed by Sebacia Inc
  - ~150 nm silica-gold nanoshells, coated with PEG
  - treat acne by disrupting overactive sebaceous glands in the skin



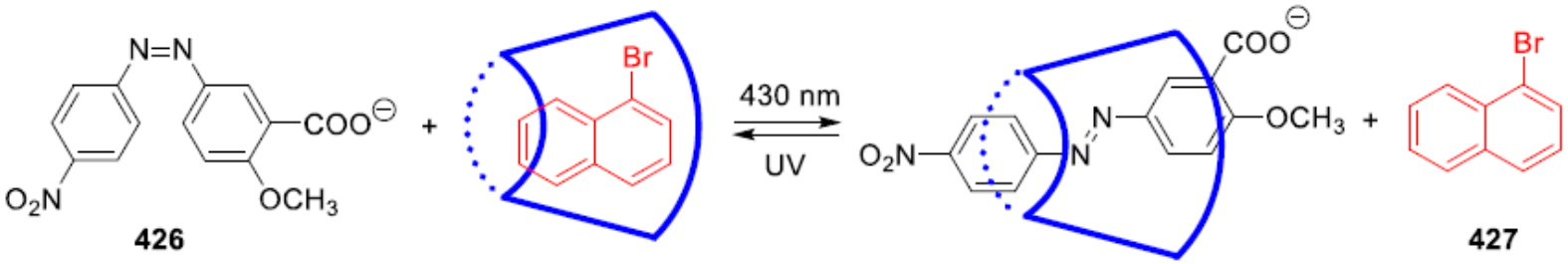
Anselmo et al. *Am. Assoc. Pharm. Sci.* 2015, 17(*5*), 1041.

Photocontrol over host-guest chemistry of cyclodextrins

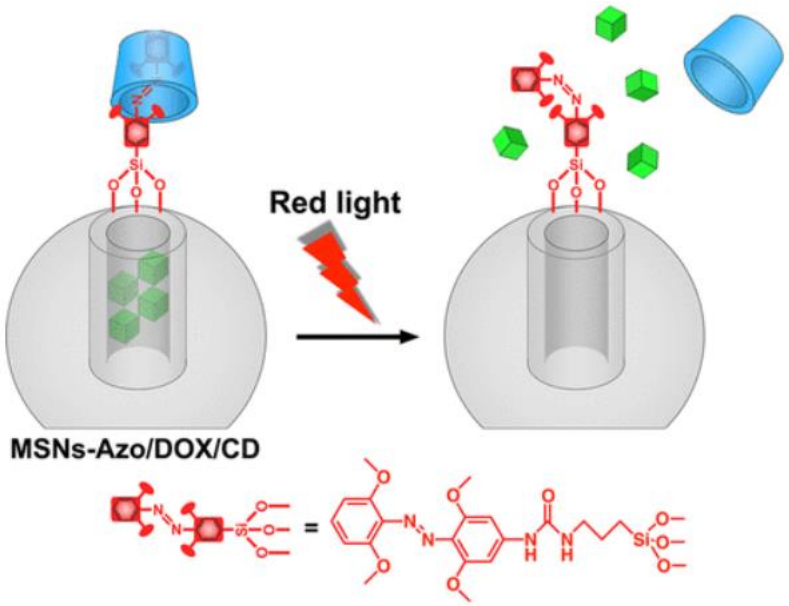
Cyclodextrin host-guest chemistry



Osa et al. *J. Am. Chem. Soc.* 1979, 101, 2779-2780.

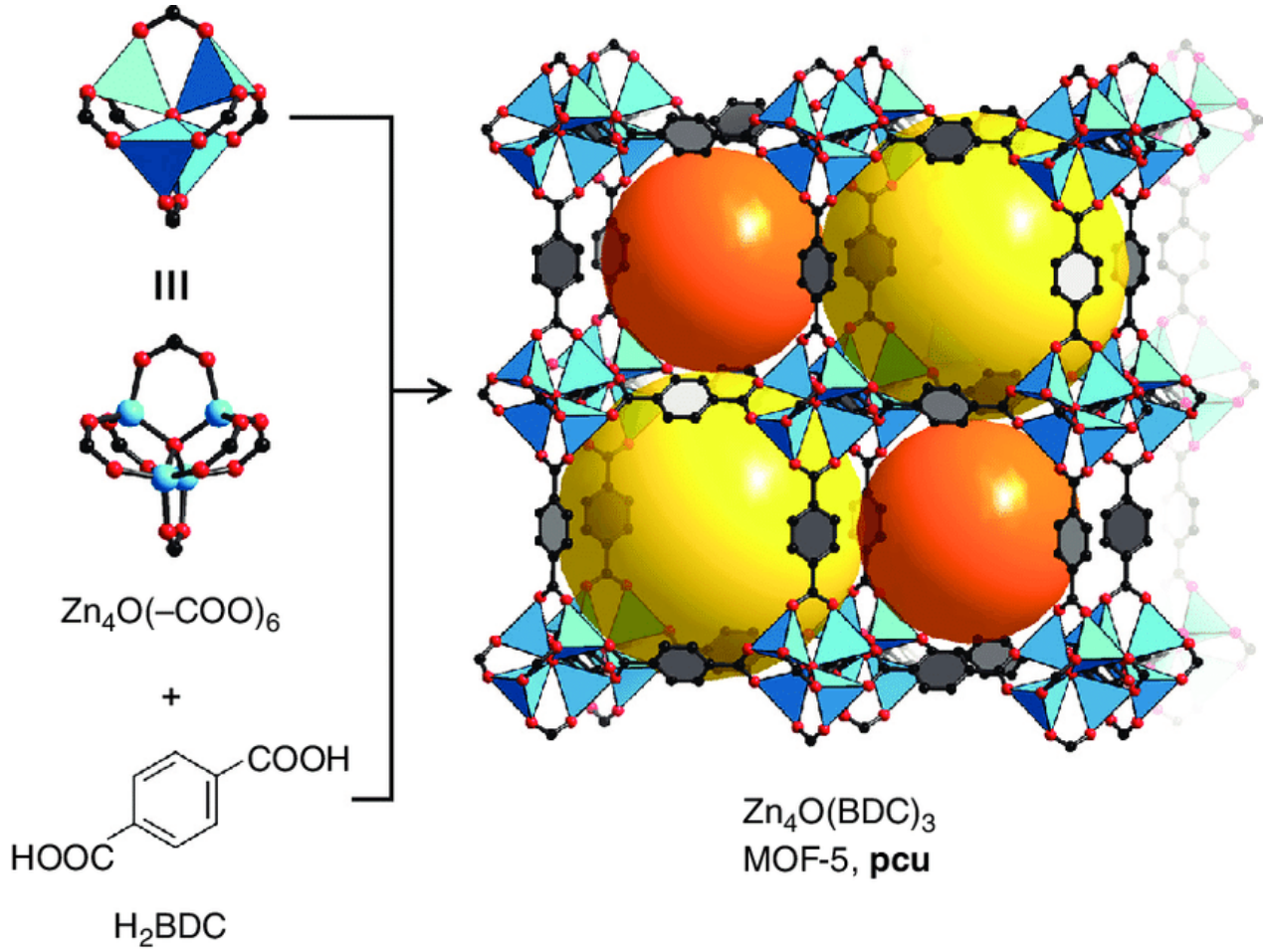


Wang and Wu constructed supramolecular valves from tetra-o-methoxy-substituted azobenzene and β-CD to control release of doxorubicin from nanopores of MSC using red light (*Langmuir* 2016, 32 (2), 632-636).



Klán et al. *Chem. Rev.* 2020, 120, 13135-13272.

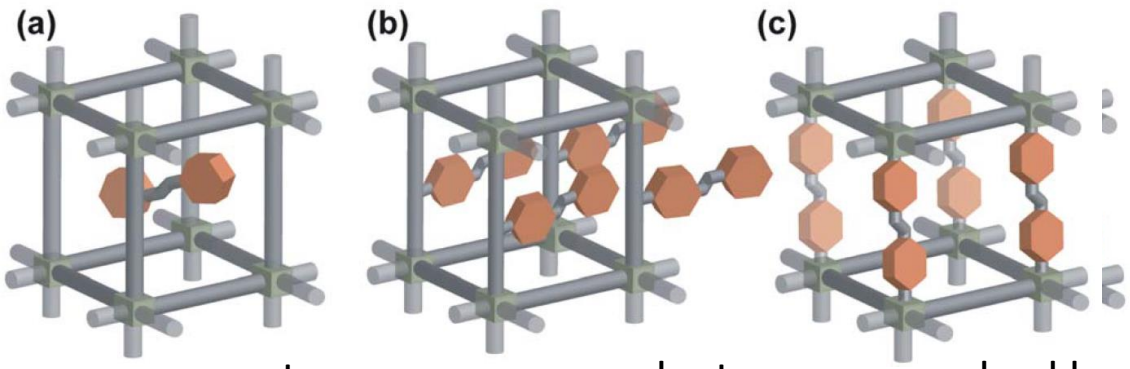
Metal-organic frameworks – MOFs (MOF-5)

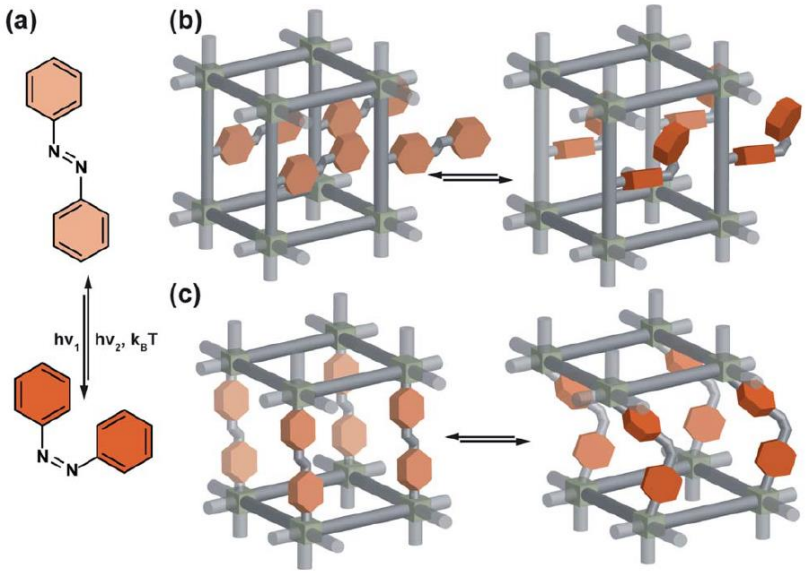


O. Yaghi, ch. 9: Macrocyclic and Supramolecular Chemistry: How Izatt–Christensen Award Winners Shaped the Field

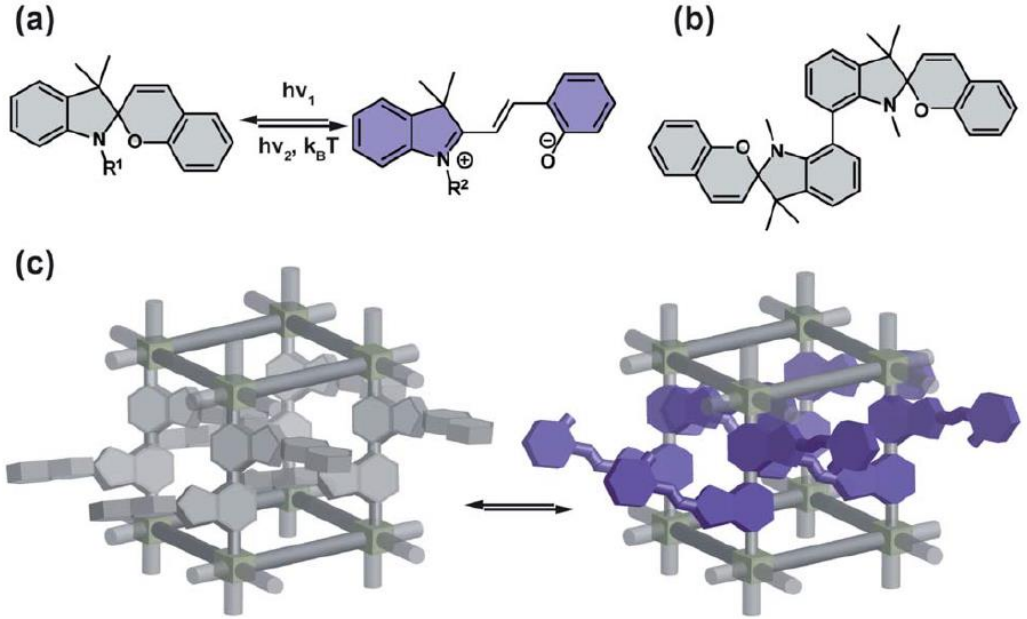
Photoswitchable MOFs

Azobenzen switches

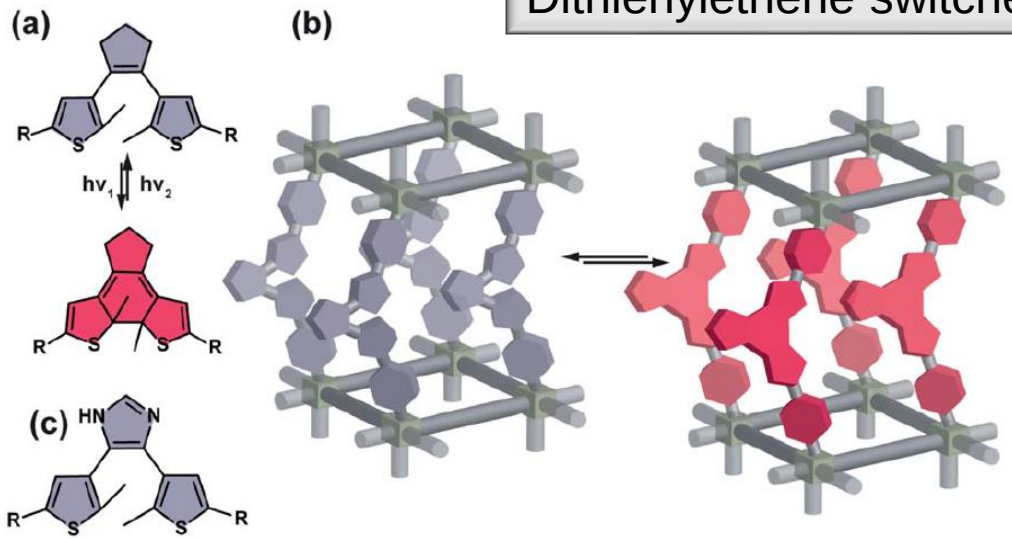




Spiropyran switches



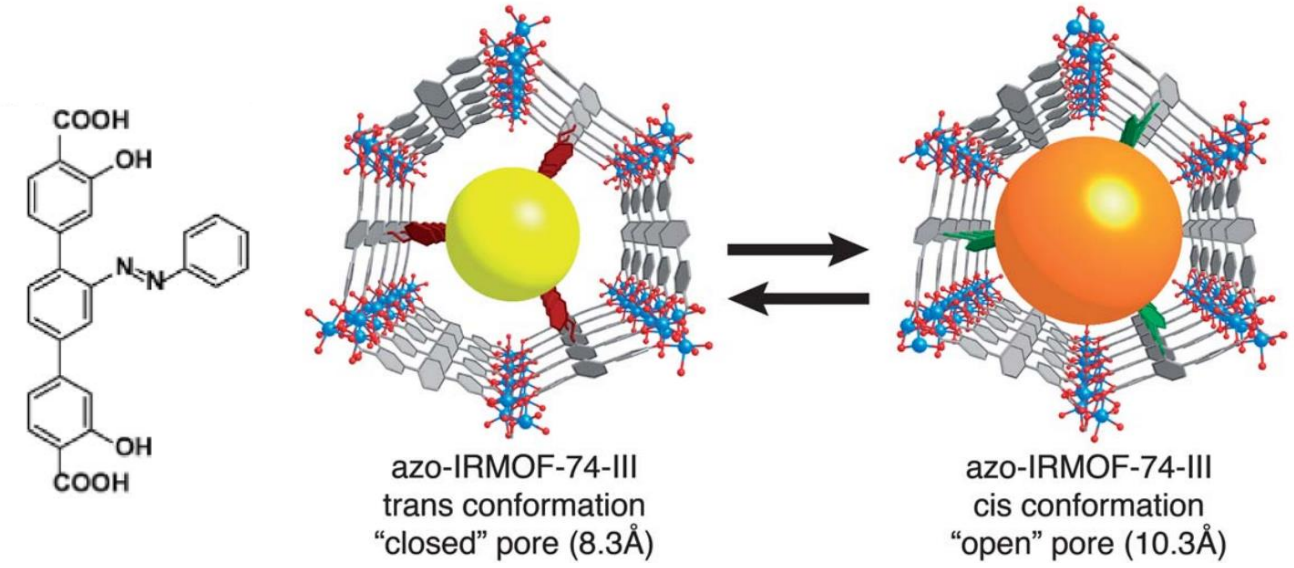
Dithienylethene switches



Feringa et al. *Nanoscale Adv.* 2021, *3*, 24–40.

Photoswitchable MOFs

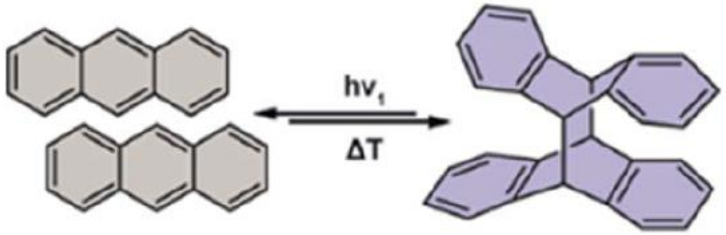
- The geometrical change *E/Z* can be used to release cargo from microporous materials
- The first ever, isoreticular MOF-74, having a one-dimensional hexagonal microchannels functionalized with evenly separated azobenzene pendants pointing towards the center of the pore
- Challenges are mode of linker incorporation, local heating, bulk isomerization



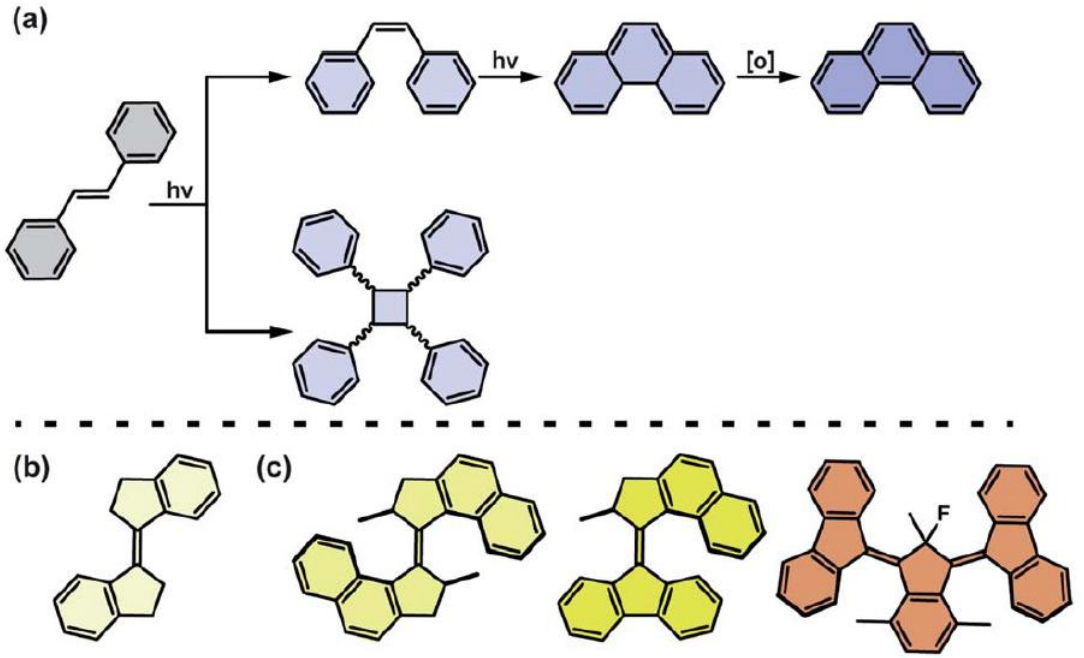
a) Feringa et al. *Nanoscale Adv.* 2021, *3*, 24–40. b) Stoddart and Yaghi et al. *Chem. Sci.* 2013, 4, 2858–2864

Photoswitches

Anthracene switches



Stilbene switches and molecular motors



Feringa et al. *Nanoscale Adv.* 2021, *3*, 24–40.

Photodruggability

- Druggability = possibility for a disease-related receptor/enzyme to be targeted by a drug (usually a small molecule) that can bind to it with high affinity and change its activity/properties

- Photodruggability = the above and:
  - target should be responsive to the light-induced changes
  - target must be related to a localized disease, such as a solid tumor or local inflammation
  - target should be accessible by light

Feringa et al. *Angew. Chem. Int. Ed.* 2016, 55, 10978–10999.

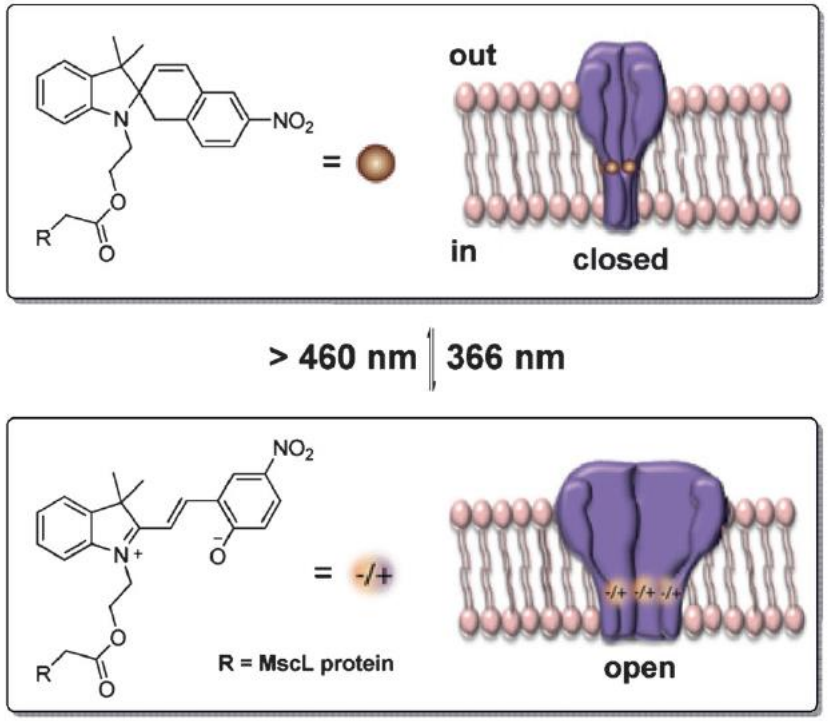
Photodruggability

- This can lead to division by accessibility of light to organs:
  - Class 1 – easily accessible, skin, eyes
  - Class 2 – accessible by endoscopy, GI tract, mouth and throat, sinuses, respiratory system, cervix, biliary tract, urine bladder
  - Class 3 – accessible through the skin without incision (lying just below the skin): thyroid, testicles, lymph nodes, muscles, and bones close to skin
  - Class 4 – accessible through minor incision: peritoneum, including pancreas, liver, ovaries, stomach, intestines, kidneys, and spleen; also prostate, most blood vessels, glands, lymph nodes, muscles, and bones
  - Class 5 – accessible through major incision or intraoperatively: brain and bone marrow

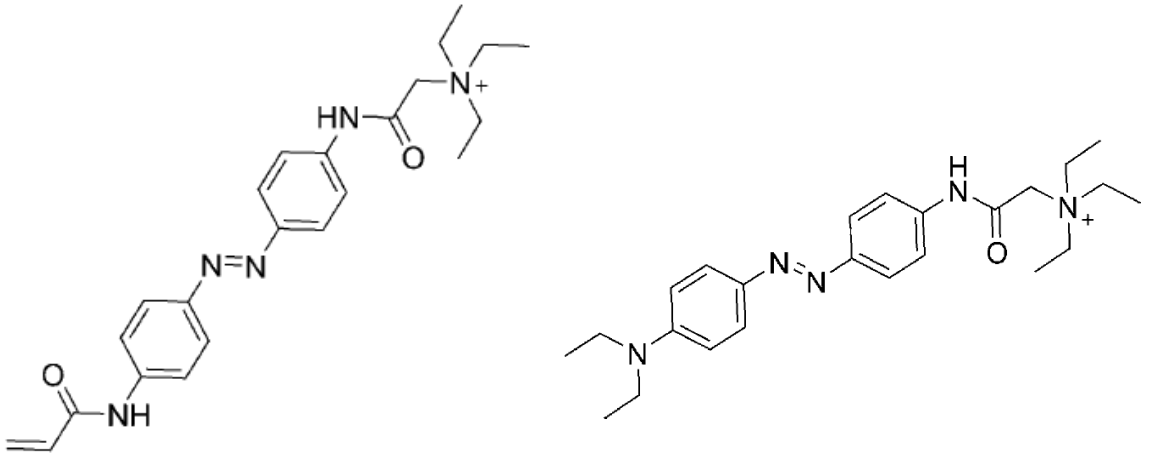
Feringa et al. *Angew. Chem. Int. Ed.* 2016, 55, 10978–10999.

Photodruggability – Class 1

- Light-gating process: formation of the (zwitterionic) merocyanine isomer leads to localized build-up of charges and, thus, opening of the channel



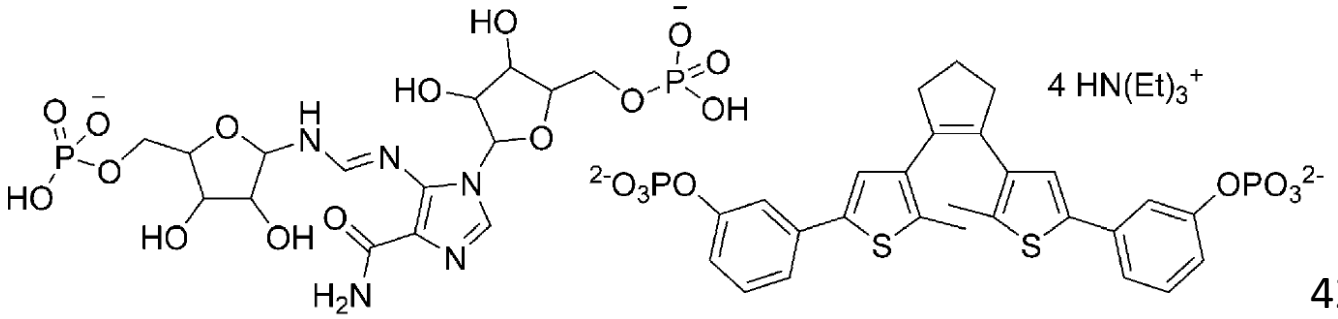
- K_V channel photoswitches that enable control of neuron excitation (blind mice vision)



Feringa et al. *Angew. Chem. Int. Ed.* 2016, 55, 10978–10999.

Photodruggability – Class 2

- Treatment of tuberculosis, *Mycobacterium tuberculosis,* phosphoribosyl isomerase A (mtPriA)



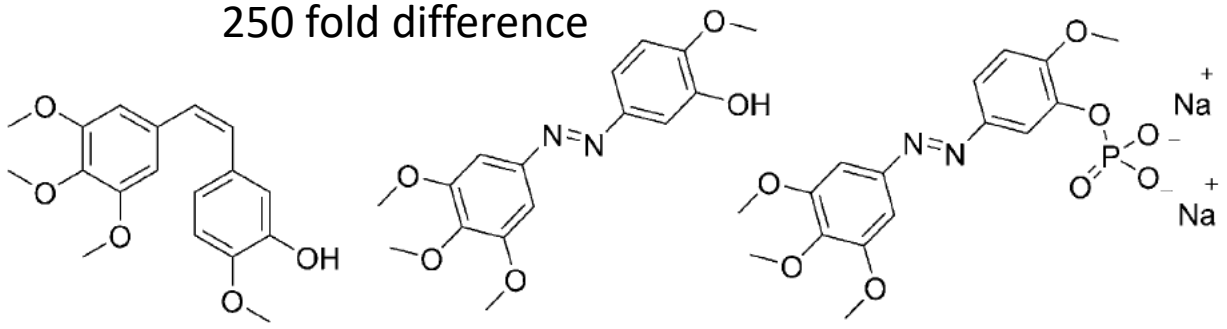
ProFAR **6**

420 nm (10 fold difference)

Photodruggability – Class 3

- Microtubule dynamics are essential in intracellular transport, motility, and cell proliferation
- Combretastatin A4 phosphate has shown potency against anaplastic thyroid carcinoma (inhibits polymerization of tubulins)

250 fold difference

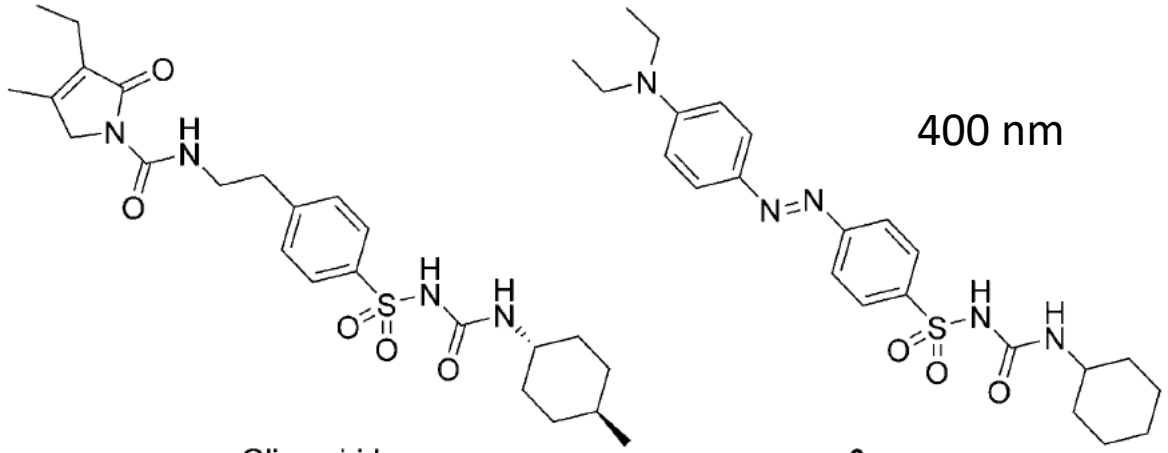


Combretastatin A4 **8a** **8b**

Feringa et al. *Angew. Chem. Int. Ed.* 2016, 55, 10978–10999.

Photodruggability – Class 4

- Diabetes research – sulfonylurea 9 allows control over insulin release and pancreatic beta cell function with UV light

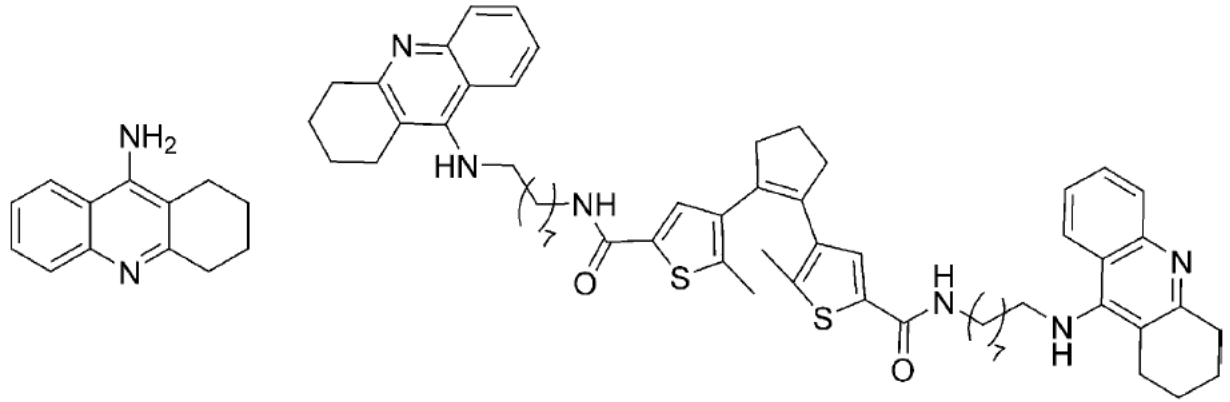


Glimepiride
Stimulates production of insulin

9

Photodruggability – Class 5

- Photocontrol of *β*-amyloid aggregation associated with Alzheimer‘s disease



tacrine (THA)
Acetylcholin esterase inhibitor
(hepatotoxic)

15

Feringa et al. *Angew. Chem. Int. Ed.* 2016, 55, 10978–10999.

In the next class…

Molecular machines

Thank you for your attention!