



New tricks and emerging applications from contemporary azobenzene research

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Abstract

Azobenzenes have many faces. They are well-known as dyes, but most of all, azobenzenes are versatile photoswitchable molecules with powerful photochemical properties. Azobenzene photochemistry has been extensively studied for decades, but only relatively recently research has taken a steer towards applications, ranging from photonics and robotics to photobiology. In this perspective, after an overview of the recent trends in the molecular design of azobenzenes, we highlight three research areas where the azobenzene photoswitches may bring about promising technological innovations: chemical sensing, organic transistors, and cell signaling. Ingenious molecular designs have enabled versatile control of azobenzene photochemical properties, which has in turn facilitated the development of chemical sensors and photoswitchable organic transistors. Finally, the power of azobenzenes in biology is exemplified by vision restoration and photactivation of neural signaling. Although the selected examples reveal only some of the faces of azobenzenes, we expect the fields presented to develop rapidly in the near future, and that azobenzenes will play a central role in this development.

Keywords Azobenzene · Photoswitching · Chemical sensing · Organic transistors · Vision restoration

1 Introduction

Azobenzenes are a class of organic molecules characterized by two phenyl rings connected by an azo bond [1]. Used originally as dyes in textile, food, and cosmetic industries, azobenzenes have in the past decades emerged as the molecules of choice when devising light-responsive “smart” materials [2]. The unique light-induced isomerization of azobenzenes between the linear, thermodynamically stable *trans* isomer and the bent, metastable *cis* isomer makes them of great interest for diverse fields of applications, such as sensing, photonics, microfabrication, electronics, biology, and many more [3–5]. Upon light absorption, the photoisomerization-induced geometrical change affects the electron distribution of azobenzenes, and therefore their affinity to certain chemical species. Azobenzene photochemistry and related applications have been studied so intensively in the last decades that one could argue that these

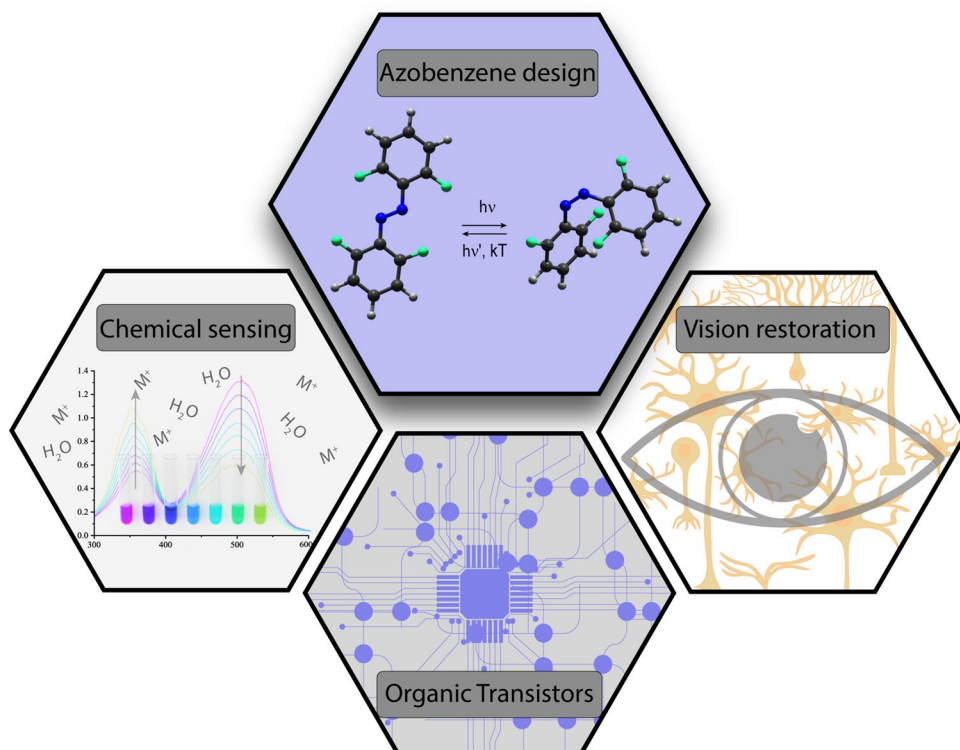
molecules do not hold mysteries anymore. However, the interest towards azobenzenes has not decreased, yet it has taken different, unprecedented directions, especially related to the integration of such photoswitches into materials for, e.g., dynamically controlling materials properties and biological phenomena [4, 6–8]. Especially the manifestations of “azobenzene photomechanics” [9] have been intensively studied, yielding photoactuatable “life-like” motions [10] and soft robotic systems [11–14] and photopatternable surfaces for photonic applications [15–17].

In this perspective, we provide a selection of the recent (~last 10 years) advancements of azobenzene research in three specific areas (Fig. 1): chemical sensing, organic transistors, and vision restoration. The fields were chosen because of their innovation potential, and because we believe that azobenzenes will play a major role in the future development in each of them. We first present the latest advancements in the molecular design of azobenzenes (Sect. 2), especially focusing on low-energy-light-absorbing, thermally stable azobenzenes. The molecular design can be tailored not only to tune *cis* lifetime and switching wavelengths, but also to detecting different chemical species in liquids and gas. In Sect. 3 the use of azobenzenes for sensing purposes will be reviewed, with particular emphasis on

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Fig. 1 Graphical representation of the research fields of choice, which stem from the azobenzene molecular design: chemical sensing, organic transistors, and vision restoration



chemical sensing and lifetime-based measurement of environmental humidity. The photoisomerization process can be used to amplify or switch electrical signals, opening a route for photoswitchable organic transistors with photocontrollable dielectric layer, active channel material, or the interface in between, to which Sect. 4 is devoted. Finally, Sect. 5 illustrates how azobenzenes can be used in restoring vision in degenerated retinas and modulating the transmission of electrical signals *in vivo* by photocontrolling ion channels activity and membrane action potentials.

2 Molecular design of azobenzenes

Azoarenes are typically robust and exhibit fast, efficient, and clean photoisomerization both from *trans* (*E*) to *cis* (*Z*) and in the opposite direction. However, when photoresponsive systems are taken beyond the proof of concept, the photo-switches giving rise to the macroscopic material response must meet ever more demanding requirements regarding their spectral properties and isomerization dynamics. For instance, the parent azobenzene absorbs mostly ultraviolet light that has low tissue penetration depth and a generally degrading effect on materials, especially living systems. Thus, modified azobenzenes that can be efficiently isomerized with visible light, preferably from the red end of the spectrum, are extensively studied. Furthermore, in many applications, high thermal stability of the metastable *cis*

isomer (i.e., slow thermal *cis*-to-*trans* isomerization) is beneficial. Herein, we will present some of the latest progress towards low-energy-absorbing and thermally stable azobenzenes. For azoheteroarenes, we recommend the recent review by König and coworkers [18].

The absorption spectra of most *trans*-azoarenes are governed by an intense π - π^* band which can be used to drive the isomerization towards *cis* (Fig. 2). The peak maximum can be red-shifted to > 400 nm with electron-donating amino substituents and even to the far-red/near-infrared region by employing the protonated methoxy- and amino-substituted azobenzenes [19]. The energy of the π - π^* transition correlates with the activation energy of thermal isomerization so that these azobenzenes isomerize from *cis* to *trans* on a timescale of seconds or less [20]. The *cis*-lifetimes are still long enough for efficient switching from *trans* to *cis* with high-intensity irradiation, and this type of instant on/off switching is beneficial for applications in, e.g., vision restoration (see Sect. 5) [21], nonlinear optics [22], and photoinduced surface patterning [23]. Traditionally, red-absorbing azobenzenes have been designed by incorporating electron-donating and -withdrawing moieties on opposite rings, most recent advances taken by Eom and Khan [24]. Such so-called push-pull azobenzenes often have short, sub-second *cis*-lifetimes and can be utilized in the aforementioned applications in which fast switching is beneficial. For some push-pull azobenzenes the *cis*-stability is so low that efficient isomerization from *trans* to *cis* is difficult. These

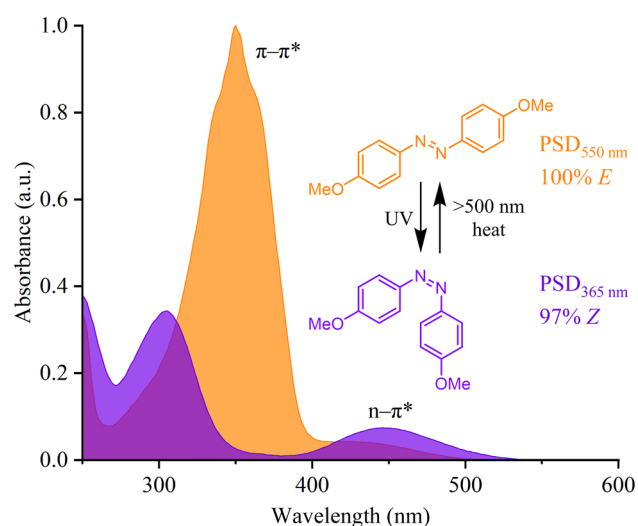


Fig. 2 Absorption spectra of pure *trans*-4,4'-dimethoxyazobenzene and a *cis*-rich photostationary state acquired upon 365 nm irradiation, depicting the π - π^* and n - π^* absorption bands

molecules can be utilized as dyes or photothermal converters in, e.g., photoactuation.

To combine visible light isomerization and good thermal stability, it is necessary to utilize the less probable but lower-energy n - π^* transition which, for most thermally stable azobenzenes, produces overlapping absorption peaks for both *cis* and *trans* isomers at around 400–500 nm. Efficient switching in both directions, i.e., high photostationary state distributions (PSDs), requires red-shifting the n - π^* band of the *trans* isomer while not affecting the excitation energy of the *cis* isomer, thus separating the bands. To this end, several molecular structures have been designed, the first example being the *ortho*-ethylene-bridged azobenzene by Herges and coworkers [25]. The molecule could be switched between PSDs of 92% *cis* and 100% *trans* with 520 and 385 nm light, respectively. Most interestingly, due to its constrained ring

structure, the *cis* isomer was more stable than the *trans*, with a moderately long thermal *trans*-lifetime of 4.5 h at room temperature. This study was soon followed by a tetra-*ortho*-methoxyazobenzene by the group of Woolley [26]. The splitting of the n - π^* bands was not as great as in the case of the ethylene-bridged azobenzene but still enabled switching between PSDs of 80% *trans* and 85% *cis* with 450 and 530 nm light, respectively. In addition to lowering the excitation energy for the *cis*-to-*trans* photoisomerization (from 385 to 450 nm), this molecular design increased the thermal *cis*-lifetime to 2.4 days.

The *cis*-stability was taken to a superior level by Hecht and coworkers with *ortho*-fluorinated azobenzenes whose *cis*-lifetimes reach months or years at room temperature, depending on the substitution pattern (**1** in Table 1) [27, 28]. Although this degree of *cis*-stability can nowadays also be accomplished with certain azoarylpyrazoles [18], no other azobenzene families are known to couple year-long *cis*-lifetimes with efficient visible-light activation. In particular, combining tetra-*ortho*-fluorination with electron-withdrawing *para* substituents, such as ester moieties (**2**) improves the isomerization efficiency, yielding PSDs near unity (>95%) in both directions upon illumination with 410 and >500 nm light. Upon longer irradiation periods (10–160 min), even the use of red light has recently been demonstrated for azobenzenes bearing ester [29] or aldehyde [30] moieties in the *para* position.

On the other hand, *ortho*-chloroazobenzenes presented by the groups of Trauner, Feringa, and Szymanski exhibit greater bathochromic shifts for the n - π^* band, allowing for lower-energy light to be utilized [31–33]. This has been attributed to their increased conformational flexibility that elongates the tail of the band on the red side. Even though the spectral separation is slightly worse than for the corresponding *ortho*-fluorinated compounds (PSDs of 90% *cis* and 85% *trans* have been reported for **3**), the absorbance reaches further towards red and *trans*-to-*cis* isomerization

Table 1 Examples of low-energy-absorbing azobenzenes and their characteristics

	$\lambda_{trans \rightarrow cis}$ (nm)	$\lambda_{cis \rightarrow trans}$ (nm)	PSD _{<i>cis</i>}	PSD _{<i>trans</i>}	$t_{1/2}$	Special feature
1	> 500	410	94	91	4 days @60 °C	Best bistability (~2 years at r.t.)
2	> 500	410	95	95	30 h @60 °C	Best PSDs
3	625	426	90	85	38 days @25 °C	Red light <i>E</i> - <i>Z</i> isomerization
4	660	410	97	90	16 h @70 °C	Red light <i>E</i> - <i>Z</i> with improved bistability
5	405	595	80	82	50 h @25 °C	Fast switching with visible light

is possible even with 625 nm irradiation. The *cis*-stability, however, is remarkably lower (half-life of 25 h in room temperature). To combine the best qualities of *ortho*-fluorinated and -chlorinated switches, Konrad and coworkers investigated the isomerization dynamics of an *ortho*-difluoro-dichloroazobenzene **4** and discovered that this mixed *ortho*-substitution pattern yielded good *cis*-stability (half life of 16 h at 70 °C, corresponding to weeks at 25 °C) as well as a bathochromic shift even greater than for the *ortho*-chloroazobenzenes [34]. They were able to drive the PSD up to 97% *cis* with 660 nm irradiation and 90% *trans* with 410 nm.

Even though the near-quantitative isomerization in both directions is impressive and this is – in the case of *ortho*-fluorinated and -chlorinated azobenzenes – coupled to virtually bistable character and red-light isomerization, there is room for improvement in the dynamics of these switches. Compared with π - π^* activation, isomerization via n - π^* excitation is typically very slow due to the low molar absorptivity in this band. This is an issue especially in the case of *ortho*-chlorinated compounds that are isomerized via illumination in the tail of the band where the absorbance is almost negligible. Thus, reaching good PSDs may take hours even with high-intensity irradiation [31, 34]. To tackle this problem, the group of Priimagi combined *ortho*-amination with -fluorination; thus, increasing the n - π^* absorptivity while maintaining good to moderate *cis*-stability [35, 36]. As the most promising example, the azobenzene **5** carrying pyrrolidino and fluoro substituents in the *ortho* position could be isomerized fast (in seconds) between > 80% *cis* and *trans* with 405 and 595 nm irradiation, respectively, while having a *cis*-half-life of 50 h at 25 °C. However, near-quantitative PSDs could not be obtained.

We note that comparing the photoswitching dynamics of different azobenzene derivatives, and photoswitches in general, is hampered by the diversity in how the different parameters are reported in the literature. This problem is most prominent in the thermal stability of the *cis* isomer. Although most applications operate at room temperature, the *cis*-to-*trans* half-lives (or lifetimes) of some photoswitch families have only been determined at elevated temperatures. In the future, it would be beneficial to either perform the thermal isomerization studies at 25 °C or to extrapolate the room temperature value from an Arrhenius plot with three or more measurements at elevated temperatures. Another quality that cannot be compared is resistance towards degradation. Even though azoarenes are typically robust, both thermal and photochemical decomposition pathways exist, depending on the environment, temperature, atmosphere and excitation wavelength [37, 38]. Multiple switching cycles have been demonstrated without noticeable fatigue for both *ortho*-methoxylated and -fluorinated compounds [26, 28]. Some *ortho*-fluoroaminoazobenzenes were also found to be stable over repeated switching cycles, but others

decomposed even upon storage [36]. Thinking of potential future applications, a study comparing the relative stability of the most promising azobenzenes in different environments would be highly beneficial.

3 Azobenzenes for chemical sensing

Although large changes to azobenzene absorption spectrum and *cis*-lifetime can be directly achieved by suitable substitution, certain substituents also make these features sensitive to molecular environment. Examples are the highly red-shifted absorbance of protonated azobenzenes in acidic environment [19] and the several-orders-of-magnitude decrease in the *cis*-lifetime of push-pull azobenzenes when moving from a non-polar to a polar solvent [39]. As large changes in optical absorption can be easily detected even by the naked eye, these features enable the use of azobenzenes as chemical sensors, which is our first highlight topic.

Colorimetric sensors are based on the spectral changes that translate to visible changes in appearance when operating with molecules that absorb in the visible wavelength range. Usually, the azobenzene used is substituted with a functional group that strongly and specifically binds to the chosen analyte and a large spectral change is seen upon binding. Quantitative detection is achieved as the absorption at a certain wavelength increases or decreases gradually with increasing concentration of the analyte surrounding the sensing material. The accuracy of determining color changes can be increased by measuring at several wavelengths. A known isosbestic point can be used as the reference and the measured absorbance is related to this reference value, increasing the robustness of the measurement against variance due to changes in sample concentration or detection light path. Such colorimetric azobenzene sensors have been used to detect several metal cations, such as Hg²⁺ [40], Al³⁺ [41], Cu²⁺ [42], Pb²⁺ [43] as well as organic molecules relevant to applications in biology, such as sugar [44] and cysteine [45]. Li et al. recently demonstrated sensors for humidity based on the deprotonation of protonated azobenzenes in azobenzene/acid binary systems [46]. Fast response of 2.3 s to full color change and tunable colors were reported, and monitoring of human breathing was raised as the most promising application.

In the past few years, colorimetric sensors with dual functionality have been reported. Gholami et al. reported on Hg²⁺ detection by strong color change from pink to blue upon binding of Hg²⁺ to a heterocyclic azobenzene [45]. The detection of cysteine was then realized utilizing the stronger binding between cysteine and Hg²⁺ that led to the dissociation of the complex between Hg²⁺ and the azobenzene compound. Balamurugan and Lee demonstrated Hg²⁺ and F⁻ detection with an aldoxime-substituted azobenzene [47].

Mercury detection was associated to unique spectral changes (see Fig. 3a) by selective dehydration and fluoride detection to those by deprotonation. Cao et al. have created a multifunctional azobenzene gelator [48]. Owing to several different binding sites, unique spectral changes shown in Fig. 3b were seen for Hg^{2+} , Fe^{3+} , Cu^{2+} . Using multi-wavelength detection, the system could arguably be used for quantitative measurement of these metal anions simultaneously. Singh et al. have demonstrated the practicality of colorimetric sensing with a simple 3D-printed support and a modern smartphone equipped with a camera [40]. This three-channel color detection, shown in Fig. 3c, enabled accurate determination of Hg^{2+} ions in 1–20 nM concentration range relevant for drinking water safety as WHO guideline sets the upper limit at 30 nM.

In addition to colorimetric sensors, some examples of other strategies for chemical sensing with azobenzenes have been reported during the last decade. Despite the low

fluorescence quantum yield in most azobenzenes, sensing relying on fluorescence occurring upon binding with suitably substituted azobenzenes has been reported for Al^{3+} [41], Fe^{3+} [50] and CO [51]. Neither the colorimetric nor fluorescent sensing rely on the key feature of azobenzenes that powers most of the current azobenzene research: the *cis-trans* isomerization. Only few examples have been published during the last decade on sensing relying on the changes on the *cis*-lifetime despite the sensitivity of push-pull azobenzenes to solvent polarity [39] and the fact that evidence of acids and metal ions reducing the *cis*-lifetime [52] have been found out decades ago. Lifetime-based detection requires more complicated time-correlated measurement of absorbance but the added robustness towards sample-to-sample variation may outweigh this deficiency in some cases. The basis of lifetime-based sensing with azobenzenes is photoexcitation of the sensing molecules with a strong pulse to *cis*, followed by monitoring the recovery of the original

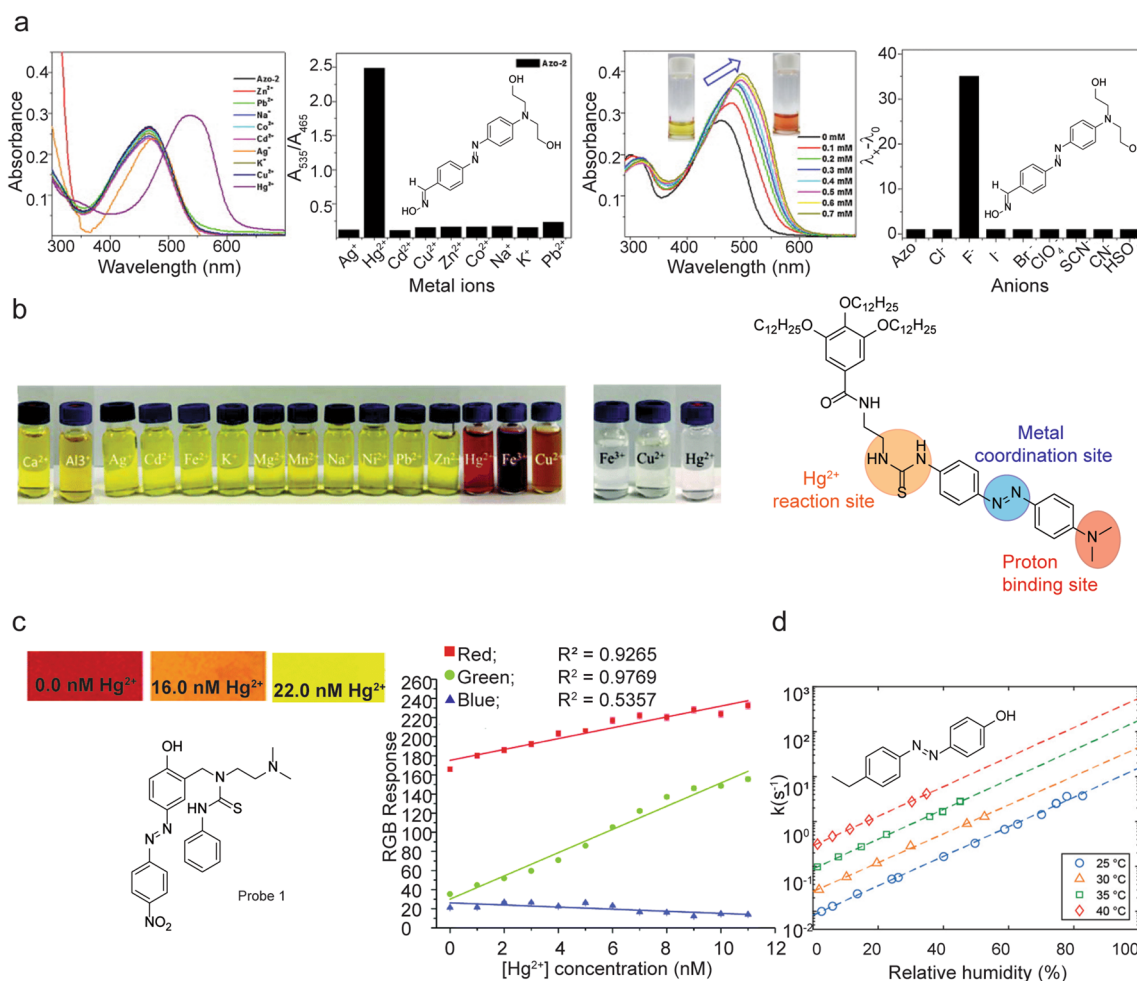


Fig. 3 **a** Specificity of sensing Hg^{2+} and F^- using a dual-sensing colorimetric sensor. Readapted with permission from Elsevier. **b** Unique color changes of a multifunctional sensing molecule. Left: solutions with azobenzenes and metal ions; Right: solu-

tions with only metal ions. Readapted with permission from Ref. [48]. **c** Quantitative sensing of Hg^{2+} using mobile phone camera and **d** relative humidity sensing using isomerization lifetime in a solid film. Readapted with permission from references [40, 49]

all-*trans* absorbance with weak, non-isomerizing probe light. Moderate changes in the isomerization kinetics have been induced by silver nanoparticles [53]. A clearer dependency of *cis*–*trans* thermal isomerization rate has been found for alkali halide salts at relatively high concentrations [54] and to bisphenol A in water in a concentration range below that allowed by food safety standards [55]. An even more pronounced and systematic dependence of *cis*–*trans* isomerization rate was found for 4-phenylazoaniline with varying H⁺ concentration (pH) [56]. Increase from 10^{−9} to 10^{−3} mol/L lead to a 5 orders of magnitude monotonic increase in the *cis* isomerization rate while also more complex dependencies on the isomerization rate were observed for other azobenzenes.

The majority of chemical sensing with azobenzenes is solution-based where both the indicator azobenzene and the analyte are dissolved into water or mixtures of water and an organic solvent, such as acetonitrile or ethanol [40–43, 45, 47]. In some cases, the indicator has been bound to a solid material by embedding to silica [40] or covalently linking it to a suitable polymer, [57] creating convenient sensors for the detection of ionic species in solution or simply used as a paint to cover glass plates to create a humidity sensor [46]. Solid polymers enable additional specificity for the sensing as demonstrated in highly selective sensing of bisphenol A by molecular imprinted azobenzene polymers [55]. Strain-dependent isomerization kinetics have been found in azobenzene-containing crosslinked elastic polymer, enabling, *e.g.*, force sensing on the level of polymer strands [58].

A notable demonstration of isomerization-kinetics-based sensing was made by Poutanen et al. who used hydroxyazobenzenes embedded in a hygroscopic polymer to measure water content of air [49]. An exponential dependence (see Fig. 3d) between relative humidity and *cis*-to-*trans* isomerization rate constant was shown at several temperatures over a wide range of humidities. The possibility to tune the humidity sensitivity by changing the azobenzene substitution pattern or concentration in the polymer thin film and stability for over 20,000 photoexcitation cycles were reported. These findings pave the way for azobenzene thin film gas sensors that are affordable due to fabrication by printing, accurate due to high sensitivity of the isomerization rate to the analyte, and readable optically with no physical contact.

4 Azobenzene-based organic transistors

Azobenzene photoswitching can be used to endow organic electronic devices with multifunctional sensing and remote control capabilities [59, 60]. Other photoswitches, such as diarylethenes, spiropyrans, and spirooxazines, have also been used in electronics, each one possessing distinct advantages [59, 61, 62]. When blended into support matrices, such as polymers, photoswitches enable reversible tuning

of the output current, conductivity, or electroluminescence of the materials by light. Due to their photocyclization, the HOMO/LUMO levels of diarylethenes can be tuned along with modulating charge carrier transport paths by altering the level of π -conjugation in the system [59]. On the other hand, spiropyrans and spirooxazines are more effective for tuning energy levels due to the drastic changes in dipole moment upon photoisomerization between ionic and non-ionic states [59]. Azobenzenes, on the other hand, possess the unique advantage of producing pronounced changes in molecular geometry upon photoisomerization, in addition to large changes in dipole moment [63]. Comparing the effectiveness of the different photoswitches is out of the scope of this perspective, but the reader is invited to refer to several comprehensive reviews recently published on the topic [59–61].

In organic field effect transistors (OFET), photochromic molecules have been used to achieve electrical UV-light sensors, where the photoswitching allows to reversibly tune the current passing through the transistor channel [59, 64]. A typical OFET is a three-terminal transistor composed of an organic semiconductor layer that bridges two electrodes, called source and drain, and a third electrode called gate, which is separated from the semiconductor by a dielectric layer (illustrated schematically in Fig. 4). When a voltage is applied between the gate and source electrodes the electric field polarizes the dielectric layer, attracting charge carriers at the semiconductor/dielectric interface within the region overlapping with the gate electrode, forming a conducting channel inside the semiconductor. Applying a voltage between the source and drain electrodes allows these charge carriers to be driven across the channel area. Three different approaches can be identified to tune the OFET performance with azobenzene moieties: (i) interfacial modification, (ii) modification of the dielectric layer, and (iii) modification of the active channel material.

We first focus on examples from previous literature on interfacial modification. Crivillers et al. modified the source and drain contacts of a bottom gate–bottom contact OFET with a self-assembled monolayer (SAM) of a thiol-functionalized biphenyl azobenzene (Fig. 4a) [65]. The air-stable perylene diimide-based *n*-type organic semiconductor PDIF-CN2 was deposited as the channel material. PDIF-CN2 was chosen as the semiconductor due to a small overlap in the optical absorption with the SAM, allowing for selective excitation of the azobenzene with UV and visible light. The highly ordered SAM exhibited a PSD of 96% *cis* on top of Au(111) that resulted in increased source–drain current and reduced threshold voltage of the OFET. The performance of the OFET could be reversibly tuned by irradiation, and the changes were attributed to the smaller tunneling barrier distance for the *cis*-form than for the *trans*-form of the SAM. Raimondo et al. further extended this concept by

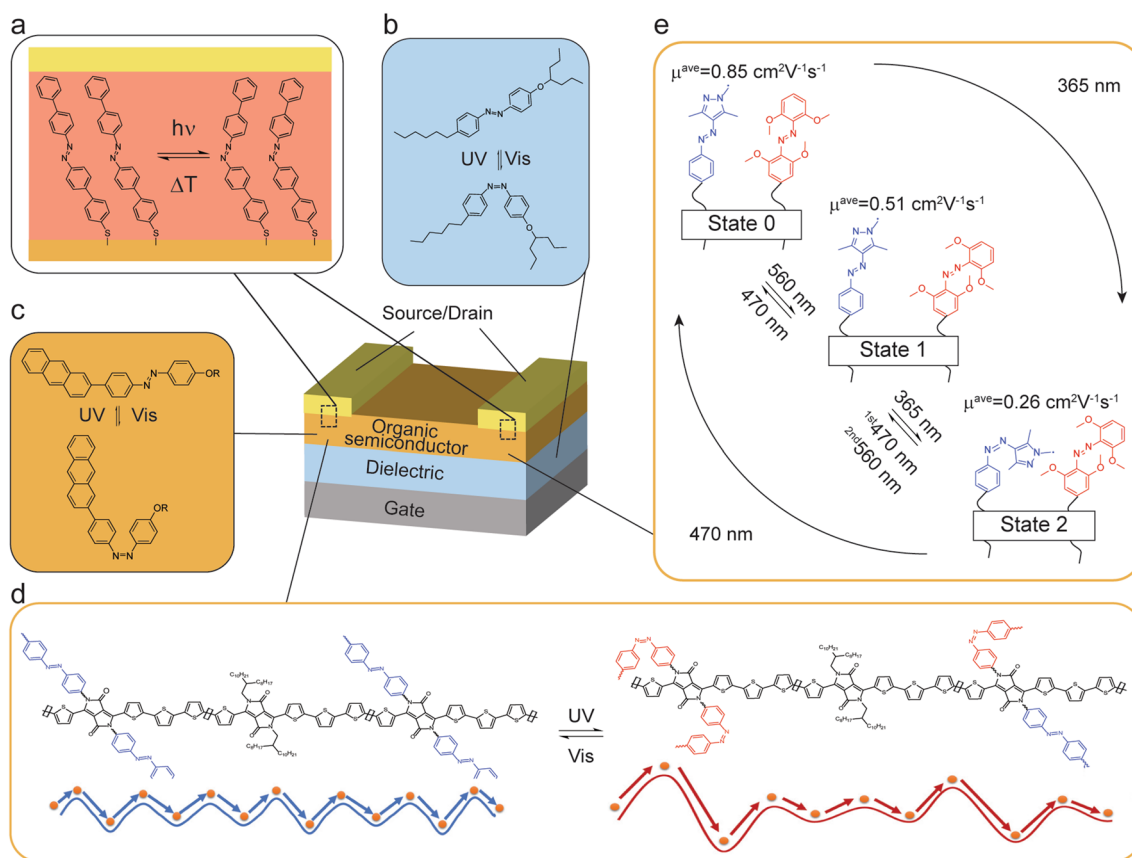


Fig. 4 Schematic illustration of a bottom-gate top-contact OFET and different modification methods with azobenzenes. **a** Interfacial contact modification by Crivillers et al. (adapted with permission from Ref. [65]). **b** Mixing azobenzene into a PMMA dielectric by Lee et al. from Ref. [69]. **c** Anthracene-based organic semiconductor chemically modified with an azobenzene moiety by Chen et al. from Ref. [72]. **d** Azobenzene side-chain modified polymeric semiconduc-

tor by Tian et al. (adapted with permission from Ref. [73]), where the *cis-trans* isomerization results in a conformational disruption of the charge transport pathways and **e** an extension of the previous work (adapted with permission from Ref. [74]) where both azobenzene and arylazopyrazole side-groups are incorporated into the polymer to enable three different mobility levels depending on the irradiation wavelength

functionalizing gold nanoparticles (AuNP) with a SAM of thiol-capped biphenyl azobenzene, followed by mixing the functionalized AuNPs into the OFET channel composed of poly(3-hexylthiophene) (P3HT) [66]. The AuNPs acted as traps for charges within the channel, with the *cis*-form reducing the tunneling barrier for trapping/detrapping. In this case UV-irradiation resulted in increased source-drain current. Tseng et al. functionalized the SiO₂ dielectric layer of pentacene-based bottom gate-top contact OFETs with azobenzene derivatives that contained either a silane group for SAM formation or a carboxylic acid linker that formed clusters of multilayers [67]. The azobenzene groups trapped charge carriers from the pentacene layer and could be triggered either photochemically or by electric gate biasing. The trapping induced electrical bistability and large hysteresis to the OFET performance. They further modified the *para* position of the azobenzene moiety to contain either H, CH₃, CF₃, or C₁₂H₂₅ groups. Either electrons or holes could be trapped depending on the substituent group (CF₃ or CH₃),

resulting in different direction threshold voltage shifts in the transfer curves. The substituent also affected the trapping efficiency depending on the ability of the group to stabilize the charge and the accessibility of the trap site. The hysteresis, response time, and retention characteristics all strongly depend on the substituent. The same team later extended on this by depositing thermally 4 nm of gold on the dielectric surface [68]. This resulted in the formation of discrete AuNPs, with the surface being as nonconductive as SiO₂. The AuNPs were functionalized with azobenzenes through a mercaptoalkoxy group, with varying *para* substitution (H, CH₃, CF₃) of the azobenzene and different alkyl chain spacer lengths. The azobenzene-functionalized dielectric layer was compared with purely insulating alkyl chains. The azobenzene moieties again trapped electrons or holes depending on the substituent, with the length of the spacer affecting the number of charges trapped. Furthermore, the retention of trapping was increased due to the charged azobenzene moieties shielding the charges in the AuNPs.

Two main approaches have been followed in studies where the focus was the modification of the dielectric or channel material: mixing azobenzene into commonly used OFET materials or chemically attaching azobenzene into the semiconductor. Lee et al. mixed an asymmetrically alkylated azobenzene at 40 wt-% into a poly(methyl methacrylate) (PMMA) matrix for the dielectric layer of bottom gate–top contact OFETs with P3HT as the active material (Fig. 4b) [69]. Benzothienobenzothiophene (C5-BTBT) is a UV-responsive semiconductor, and they found that the azobenzene moieties acted as efficient trap states for the charges photogenerated in the C5-BTBT. This resulted in the azobenzene moieties enhancing the UV response and could either extend or decrease the decay time of the trapped charges for different applications depending on respective HOMO–LUMO level differences between C5-BTBT and azobenzene.

Azobenzenes have been chemically attached into both small molecular and polymeric semiconductors used as the active channel material in OFETs. Arlt et al. studied OFETs based on the amorphous azobenzene glass diphenylaminoazobenzene and its dimer form. The dimer exhibited bipolar transport with similar hole and electron mobilities in the linear region [70]. As a result of irradiation with 1.4 mW/cm² intensity blue light, the threshold voltage shifted to more negative value and the hole mobility decreased by one order of magnitude. The drain current could be reversibly decreased to roughly one third of the initial value in 2.1 s, returning to the initial value in 1.3 s in dark. The mechanism behind the decrease in the current was assigned to the hole transport level being shifted up in energy upon *trans*–*cis* isomerization, resulting in trap states for transport along with a reduced amount of percolation pathways. Nakagawa et al. synthesized a nitroxide radical containing naphthalenediimide with an azobenzene moiety [71]. Even though the mobility of the bottom contact–bottom gate transistors was low, the *n*-type OFET could be reversibly switched with UV irradiation so that the threshold voltage shifted towards lower value while the electron mobility decreased to approximately half of the original value. Chen et al. functionalized anthracene with an azobenzene containing a long alkoxy group (Fig. 4c) [72]. The azobenzene resulted in reversible increase in the OFET mobility and decrease in threshold voltage after UV irradiation. When combining the UV photoresponse with the liquid crystalline phase arrangement of the alkoxy groups after annealing, they reached a high FET mobility of 0.875 cm² V⁻¹ s⁻¹.

Tian et al. modified a semiconducting diketopyrrolopyrrole-quaterthiophene polymer with alkoxyazobenzene side groups (PDAZO) [73]. The azobenzene groups underwent *trans*–*cis* isomerization that resulted in 80% decrease in source–drain current after 28 s of UV irradiation. The current was reversibly recovered after visible light irradiation.

The large photoinduced changes in current were attributed to increased energetic disorder that retarded charge transport and perturbed the interchain packing and crystallinity due to conformational changes (Fig. 4d). Later the same group incorporated two different azobenzenes, tetra-*ortho*-methoxy substituted azobenzene and arylazopyrazole, into the same conjugated polymer backbone as in PDAZO (Fig. 4e). This resulted in three different semiconducting states due to selective isomerization of the methoxyazobenzene with 560 nm irradiation, isomerization of both azo compounds with 365 nm irradiation and the reversible recovery of both with 470 nm irradiation [74]. The decrease in current after 565 nm irradiation could be tuned from 10 to 60% by changing the ratios of the methoxyazobenzene to arylazopyrazole in the side groups. With all ratios the decrease in current was around 60–70% after 365 nm irradiation. Owing to the relatively stable *cis*-forms possessing long lifetimes, the different semiconducting states were quite stable even after 60 h storage in the dark. The three states had average mobilities of 0.85, 0.51, and 0.26 cm² V⁻¹ s⁻¹ after 470 nm, 560 nm, and 365 nm irradiation, respectively. This allowed for three-value logic gate function depending on the variation of the irradiation wavelength (illustrated in Fig. 4e).

Azobenzenes have also been used for the purpose of miniaturizing OFETs down to the molecular scale. Tang et al. utilized azobenzene to modulate the charge carrier density in 2D graphene field effect transistors (GFET), illustrated in Fig. 5a. They decorated an atomically thin amino-terminated carbon nanomembrane with azobenzenes and transferred it on top of a GFET channel [75]. The nanomembrane formed a van der Waals heterostructure with the graphene layer and acted as a ~1 nm thin interposer. The azobenzene moieties could be reversibly switched with UV and visible irradiation. The isomerization to *cis*-form induced an effective electric field that acted on the GFET channel, effectively *n*-doping it. Zhao et al. functionalized 1D single-wall carbon nanotube field effect transistors (CNTFET) with two different pyrene-tethered Disperse Red 1 (DR1) derivatives that had large internal but oppositely orientated dipole moments [76]. The on–off ratios of the CNTFETs were preserved after functionalization with little to no degradation in the on-current. Threshold voltage shifts were also observed after functionalization, with a marked difference depending on the dipole moment of the used chromophore. Finally, Meng et al. used azobenzene in a single-molecule transistor that consisted of a terphenyl aromatic chain junction between graphene point contacts (Fig. 5b) [77]. The transistor operated in two different modes, one based on asymmetric stochastic conductance switching via electric field induced isomerization of the azobenzene and the other based on reversible photoswitching at low bias. The transistor could be switched between the on and off states since *trans* and *cis* isomers had different resistivities, with the *cis*-form having higher conductance.

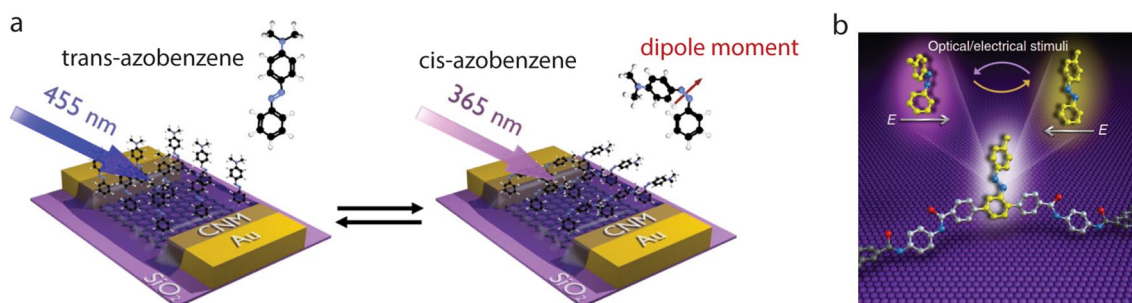


Fig. 5 **a** Effective doping of a 2D graphene field effect transistor with an azobenzene-based interposer, reproduced with permission from Ref. [76]. **b** Single molecule transistor with an azobenzene moiety, reproduced with permission from Ref. [77]

This report provided useful insights for devising chemically-gated, reversible, two-mode single-molecule transistors.

5 Azobenzene in vision restoration and investigation of neuronal signaling mechanisms

Azobenzenes have also found use in a growing field of biomedical research often referred to as photopharmacology or synthetic optogenetics [6, 78]. This field of research, conversely to optogenetics that involves natural molecules, implements synthetic photoswitches to control biological functions, such as protein conformation or cell membrane permeability, with light. Many biological functions have been studied so far with the aid of azobenzene photoswitches, such as ion pumps, enzymes, and cytoskeletal assembly, among others [6]. Herein, we will discuss only the latest developments and the many challenges awaiting vision restoration and neuron signaling studies, two exemplary applications showcasing the potential of azobenzene photoswitches in photopharmacology.

Intercellular communication via ion exchange is at the basis of multiple biological events such as neuronal signaling and vision. A simple photoisomerization reaction (from the 11-*cis* retinal to the all-*trans* retinal) initiates a cascade of events in which ion channels close, cells hyperpolarize and ultimately neurotransmitters release towards the optical nerve halts, therefore stopping inhibitory effect on retinal ganglion cell stimulation and visual perception (Fig. 6a) [79]. Degenerative pathologies of the retina may cause blindness due to an irreversible damage or loss of the retinal photoreceptors, i.e. rods and cones, controlling ion fluxes, while other cell types may be unaffected [80]. In this context, the aim of photopharmacological interventions is the substitution of rod and cone function, i.e. light-to-electric energy transduction, by a synthetic photoswitch. Light-responsive molecules that undergo geometrical changes upon light absorption allow the precise, remote control over

such biological processes. Azobenzenes are the most used synthetic photoswitches in vision restoration research, as their light-induced isomerization resembles the isomerization reaction of the receptor proteins occurring in photoreceptor cells [81]. Azobenzene-containing drugs can associate to the cell membrane and regulate light-induced ion channel activity by modulating the interaction between ion channel proteins by *trans*–*cis* isomerization.

Photopharmacological blindness treatments are distinct from other approaches (e.g. retinal chip implants, embryonic stem cell injection, and transfection with genes encoding optogenetic proteins) [82–84] as they do not require invasive surgery nor administration of exogenous proteins that may have secondary unwanted effects and cause inflammation. So far, two different methods have been developed, relying either on diffusible photochromic ligands (PCLs, also referred to as one-component approach) or protein-tethered ligands (PTLs—also referred to as two-component approach) (Fig. 6b) [85]. Around 10 years ago, the groups of Trauner and Kramer reported the use of acrylamide–azobenzene–quaternary ammonium (AAQ) as diffusible drug for vision restoration (Fig. 6c) [86]. AAQ is a K⁺ channel photoactuator that enables the control of cellular excitability by UV light (380 nm). Back-isomerization to the *trans*-form happens slowly in the dark and much faster if excited at 500 nm. The authors reported that intraocular injection of AAQ restores light sensitivity (synaptically amplified response) as well as behavioral responses (light avoidance) in vivo in mice models affected by retinitis pigmentosa [77]. Later on, modified versions of azobenzene-based quaternary ammonium photoswitches (e.g. DENAQ, BENAQ) have been implemented for the photocontrol of voltage-gated ion channels, enabling light-controlled firing of action potentials in retinal ganglion cells [87, 88]. Here, the acrylate moiety was substituted for instance by a diethylamino and benzylethylamino groups, showing improved specificity. Furthermore, they implemented red-shifted azobenzene cores, allowing excitation in the visible range (e.g. 480 nm) with quicker relaxation. In all these examples,

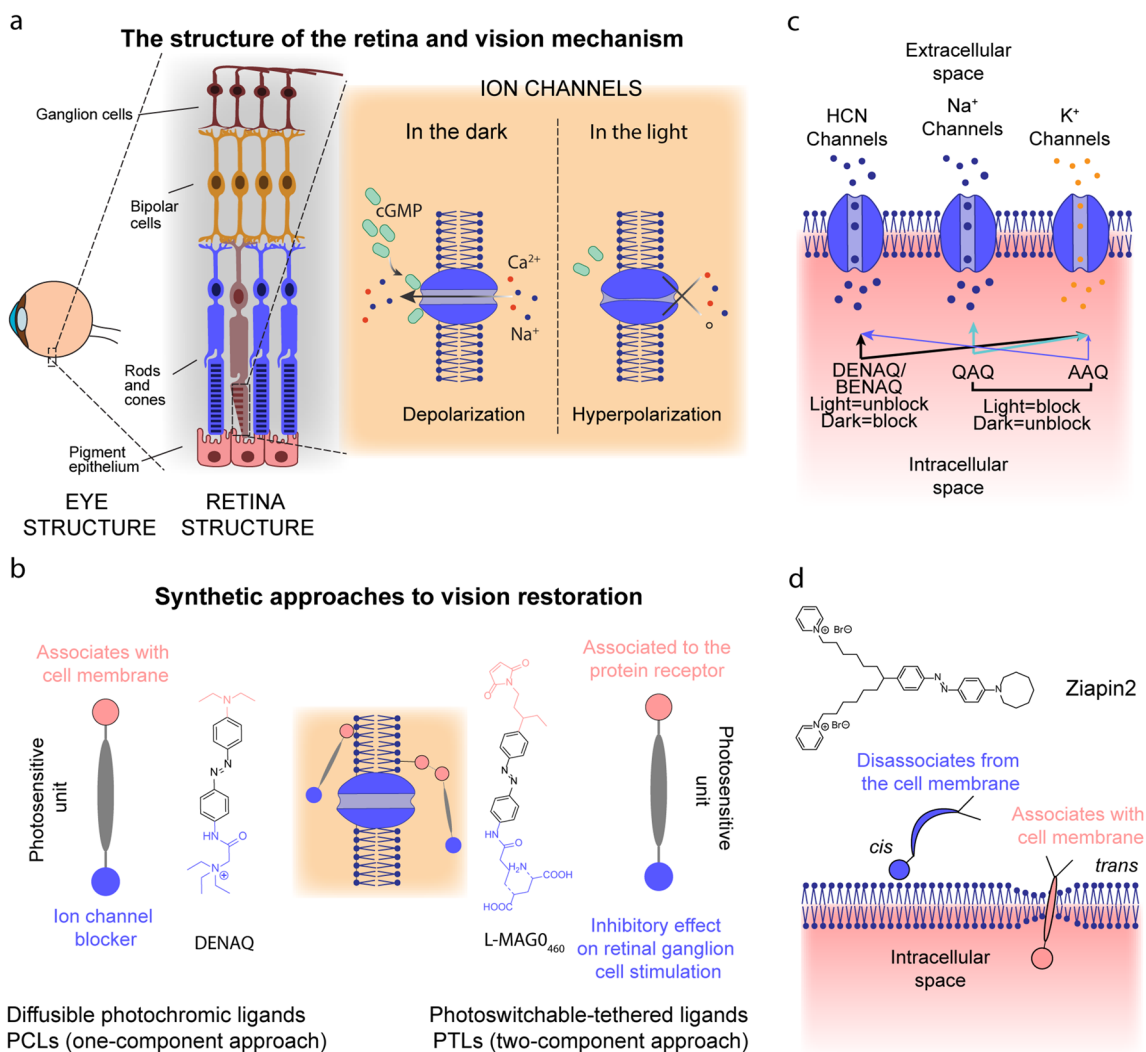


Fig. 6 **a** The structure of the retina and ion channels behaviour in vision. **b** Different azobenzene strategies used for vision restoration and their interaction with ion channels. **c** Diffusible photochromic ligands interaction with hyperpolarization-activated cyclic

nucleotide-gated (HCN) channels, sodium, and potassium channels. Adapted with permission from reference [87]. **d** Method of interaction of Ziapin2 with cell membrane upon photoswitch [94]

the light-responsive drug is composed of a photosensitive azobenzene unit in the middle, decorated by a side moiety that associates with the membrane in proximity of membrane receptors (e.g. dimethylamine, acrylamide), and another one blocking the ion channel functions (quaternary ammonium). This class of molecules can be active either in the *trans* or in the *cis* state, depending on the specific design. Whereas such drug design in its simplicity is more likely to get a faster approval for clinical use, it lacks specificity towards ion channel proteins and; therefore, has lower efficiency. Another potential drawback is that one-component approaches are temporary and would require continuous dispense of the drug to maintain restored vision.

Two-component approaches, instead, are based on synergistic combination of genetical modifications to protein

receptors (making azo-drugs highly specific to the target protein) and intraocular injections of the photoswitchable drug (e.g. maleimide-azobenzene-glutamate—MAG). The drug associates via a bioconjugation reaction to the protein receptor structure, such as maleimide moiety to a cysteine genetically introduced in the target (e.g. light-gated glutamate receptor, LiGluR). In this way, the photoswitchable drug isomerization under light irradiation affects the function of that target receptor, controlling ion currents and membrane polarization in a very specific way. On the downside, PTLs require transfecting the cell with genetically encoded binding targets [85].

The intrinsic toxicity of UV light for cell biology studies, together with its low penetration depth into biological tissue, and its strong attenuation by the human eye lens are driving

Table 2 Main challenges awaiting azobenzene research regarding molecular design, chemical sensing, organic transistors, and vision restoration and signaling

Molecular design	Chemical sensing	Organic transistors	Vision restoration and signaling
Fast and quantitative switching between two thermally stable states with low-energy light	Multifunctional sensing with orthogonal azobenzenes	OECT with light-controlled properties	Vision restoration in congenital/inborn blindness
Application-specific switchable functionality and compatibility	Realization of miniature spectrometers	Utilization of redox-isomerization	More diffused use of human models
Solubility, biocompatibility, and stability	Rational design of molecules for lifetime-based sensors	Controlling charge transport between azobenzenes	Color recognition, shape vision, and neural computation of visual inputs with multiple photoswitches

research towards alternative, red-shifted azobenzene drugs [89]. Furthermore, when it comes to using photoswitches for vision restoration, a faster relaxation of *cis* isomers is beneficial, as it mimics much more closely the native temporal firing patterns. Starting from the commercially available Disperse Red 1, researchers have expanded the MAG photoswitches family synthesizing second-generation PTLs characterized by red-shifted absorption with short-lived *cis* isomers [21]. Furthermore, making the azo-drugs sensitive to 2-photon excitation (2PE) using near infrared (NIR) light is an asset. NIR penetrates more in the tissue and 2PE has higher spatial resolution if compared to the one-photon process. To increase the 2PE sensitivity of PTLs, researchers need to improve the 2PE cross-section of the molecules, sometimes sensitized by a light-harvesting antenna [90, 91]. The possibility to use NIR 2PE in combination with digital holography techniques allows the parallel excitation of the field of view, compatibly with short-lived azobenzenes, enhancing their efficiency [92].

Red-shifted azobenzenes with long *cis* lifetimes and good spectral separation of the two isomers in the visible region seem to be very promising for gene expression and neuronal signaling control [80]. In these applications, there is a need to promote the expression of certain genes (~ 10 h) or silence the activity of specific neurons for a long-term experiment (~ years) [93]. Tetra-*ortho*-fluorinated azobenzenes have been used for the first time in photopharmacology to reversibly block voltage-gated ion channels [93]. Passlick et al. synthesized a symmetric bis-quaternary ammonium derivative of a tetra-*ortho*-fluorinated azobenzene whose photoswitching activity was tested *in vitro*. Its isomerization was studied also in response to 2PE in neurons. We might expect that red-shifted bistable azobenzenes will be more and more involved in the development of photopharmacological drugs. Up to now only a handful of studies report the use of *ortho*-substituted azobenzenes for this purpose and the stability of such molecules in the physiological environment was not always successful, suggesting that increasing effort is needed to establish this approach in the bio-field.

Recently, a study from Lanzani and co-workers exploited a different approach for neuron signaling studies based on an amphiphilic azobenzene photoswitch to associate with the cell membrane and regulate its capacitance provoking firing of action potentials in response to millisecond-pulse visible light (Fig. 6d) [94]. The molecule used in the work, Ziapin2, interacts with the lipid bilayer of the cell membrane via two ionic-terminated alkyl chains. Here, the azobenzene allows to fold/unfold the hydrophobic azepane moiety on the other side of the photoswitch via light irradiation. This mechanism induces membrane thickness reduction, which increases the capacitance through *trans*-dimerization and, therefore, generates a transient hyperpolarization.

6 Conclusions and future challenges

The aim of this Perspective is to provide selected highlights from the latest research, and anticipate which challenges may await in azobenzene research, from the design and synthesis of new, high-performing azobenzenes to the requirements needed for producing actual breakthroughs in the fields discussed herein. By synergistic cooperation between chemists, physicists, and engineers, we foresee a continuous development of azobenzene-based technologies (see Table 2).

Despite the progress made in the tuning of azobenzene photoswitching dynamics during the last decade, especially by employing *ortho* substituents, the azobenzene structure that would enable fast and quantitative switching between two thermally stable states with low-energy light remains elusive. It is unclear whether this can be accomplished on the same line of research or through more novel approaches. Furthermore, in addition to having optimal photochemical properties, the azobenzenes utilized in real-life applications must be compatible with the application-specific environment. Because substituents responsible for improving the photochemical qualities of the switch also

affect other vital properties, such as solubility and biocompatibility, it is unlikely that an azobenzene structure suitable for all possible application areas can be found. For example, *ortho*-substitution reduces the planarity of azobenzenes, making their orientation worse in liquid crystalline materials. Electron-poor azobenzenes, on the other hand, are rapidly reduced by glutathione, hampering their use in biological contexts. Thus, we envision that the design of new azobenzene derivatives remains valuable for the photoswitching community, even if the photochemical properties of new azobenzene derivatives would not surpass the state-of-the-art.

The emerging multifunctional sensing with azobenzenes coupled with affordable multi-wavelength detectors may open new paths for colorimetric sensing. Such detection is enabled by state-of-the-art miniature spectrometers or even the three-channel detectors present in smartphone cameras carried in everyone's pocket. We speculate that these cameras coupled with suitable low-cost gratings will turn into capable hyperspectral sensors and enable quantitative measurements beyond the capabilities of human eyes with colorimetric sensors. Combined with a handful of single- or multi-species sensitive materials, measuring water safety, for example, may take a leap in availability and cost. We also see lifetime-based sensing with azobenzenes to be only at its infancy with an interesting future ahead. Lifetime, as compared to color, is easy to quantify and less sensitive to sample-to-sample variations, the drawback being that measuring dynamic absorbance complicates measurements over color determination. For lifetime-based sensing, accurate control of the lifetime in the targeted range of analyte concentration becomes crucial; too slow isomerization (minutes) leads to long measurement times and too fast isomerization (sub-ms) requires powerful light sources and fast electronics, adding to cost. Lessons learned from the molecular design of azobenzenes on how to separately control the isomerization lifetime and other molecular properties, such as absorption spectrum and binding to the desired analyte, pave the way for rational design of molecules for lifetime-based sensors.

Azobenzenes have been incorporated in creative ways to tune the performance of OFETs, with the light-induced isomerization either increasing or decreasing the performance depending on the application. In most of the cases where azobenzene is incorporated into the active channel material, isomerization inhibits charge transport by disturbing the percolation pathways. However, there are few examples where the azobenzene has been directly incorporated into the moiety responsible for charge transport. Incorporating azobenzene into the backbone of polymeric semiconductors could be utilized to increase the control over the charge transport by directly affecting the intrachain electronic properties. Furthermore, the isomerization of azobenzene can

also be catalytically induced electrochemically [95]. This indicates that azobenzene-containing organic semiconductors may endow organic electrochemical transistors (OECT) with light-controlled properties. OECTs are an emerging type of organic transistors, where the conductivity of the transistor channel is modulated via electrochemical redox reactions. They have gained increasing interest in recent years for low-power applications, such as bioelectronic sensors due to their high transconductance values at low operating voltages in the sub-1-volt range. The electrochemical redox reactions in OECTs could simultaneously trigger isomerization pathways for the azobenzene moieties, affecting the transistor performance.

As we can see from the examples reported in the last section, pharmacological vision restoration is only possible in animals with degenerated photoreceptors and not when rods and cones are intact (congenital/inborn blindness). The potential of this approach is huge, but still many improvements are needed, eventually combining the two areas discussed herein. For instance, there is no complete understanding of how the non-native stimulation of retinal ganglion cells would allow a correct interpretation of the image by the vision processing centers of the brain. Even if characterized by reduced visual acuity and dichromatic vision, mice models have been preferred to more sophisticated models for studying vision since many genetic tools are available for mice nowadays. Further studies on color recognition, shape vision, and neural computation of visual inputs by the brain are indeed expected, combining the use of multiple photoswitches with tailored photochemical and photobiological features.

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Declarations

Conflict of interest The authors declare no competing interests.

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