ARTICLE

Azophotoswitches containing thiazole, isothiazole, thiadiazole, and isothiadiazole

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We report a novel class of azophotoswitches incorporating various five-membered heteroaryl units, such as thiazole, isothiazole, thiadiazole, and isothiadiazole. These azophotoswitches were developed through an initial screening of 24 compounds using DFT calculations to identify those with the wavelength of maximum absorption (λ_{max}) at long wavelength. Subsequently, eight selected azophotoswitches were synthesized. Compounds containing both thiazole and isothiazole moiety showed relatively long λ_{max} compared to the other synthesized compounds. This azophotoswitch exhibited reversible isomerization under visible light irradiation at 430 nm, 450 nm, 470 nm (*trans* to *cis*) and 525 nm (*cis* to *trans*). Analysis of the X-ray crystal structures of the *cis* isomer of phenylazo[1,3,4-thiadiazole] exhibited a unique orthogonal geometry.

Introduction

Photoswitches are molecules that exist in two isomers, which can be interconverted reversibly by light irradiation. Many kinds of photoswitches have been developed and used for applications in material and biological sciences.[1,2] In the case of a well-studied azobenzene photoswitch, the wavelength of maximum absorbance (λ_{max}) is at ~320 nm and undergoes *trans* to *cis* photoisomerization by 365-nm UV light irradiation. The *cis* to *trans* reverse isomerization occurs thermally or photochemically. The λ_{max} of azobenzene can be changed to longer wavelength by introducing substituents at its phenyl ring, however with a compensation of the thermal stability (half-life) of the *cis* isomer.[3-5]

Recently, azophotoswitches containing "heteroaryl" units are increasingly getting attention due to their unique light absorption and photoisomerization properties.[6] Especially, photoswitches having five-membered "heteroaryl" units showed quite different photophysical and structural properties.[7] Previously we and others reported photoswitches that contain five-membered "heteroaryl" units such as pyrrole, pyrazole, imidazole, isoxazole, triazole, thiazole and thiophene.[8-18] Each of these photoswitches have shown photophysical properties mostly affected by the type of "heteroaryl" units present. For instance, a phenylazopyrrole derivative require UV light for *trans—cis* isomerization, but the half-life of its *cis* isomer was exceptionally long.[19,20] In our recent case, the phenylazothiazole showed λ_{max} of 364 nm, 44 nm red-shifted compared to the λ_{max} of azobenzene and can isomerize by visible light (405 nm) irradiation with moderate decrease in the half-life of its *cis* isomer (2.8 h in acetonitrile at 25°C). Based on this finding, in the current study, we focused on the design of novel photoswitches that contain unexplored 5-membered heteroaryl units like oxazole, isothiazole, thiadiazole and isothiadiazole. Many pharmacologically active compounds contain one or more units of five-membered heteroaryl groups [21-25] and their photoisomerizable forms can be useful for application in photopharmacology. In this study, we used density functional theory (DFT) calculations to predict the λ_{max} of photoswitchable molecules, and our findings show a close match between the calculated data and experimental results. We found that incorporation of both thiazole and isothiazole groups in the photoswitches results in a shift of λ_{max} to longer wavelength than those of the other compounds studied. Furthermore, X-ray crystal analysis shows that the *cis* isomer geometry of phenylazo[1,3,4-thiadiazole] adopts a unique orthogonal configuration, supported by the theoretical calculation.

Results and discussion

Synthesis

We designed 24 photoswitchable molecules that has S, N or O heteroatom in the five-membered aromatic ring and conducted

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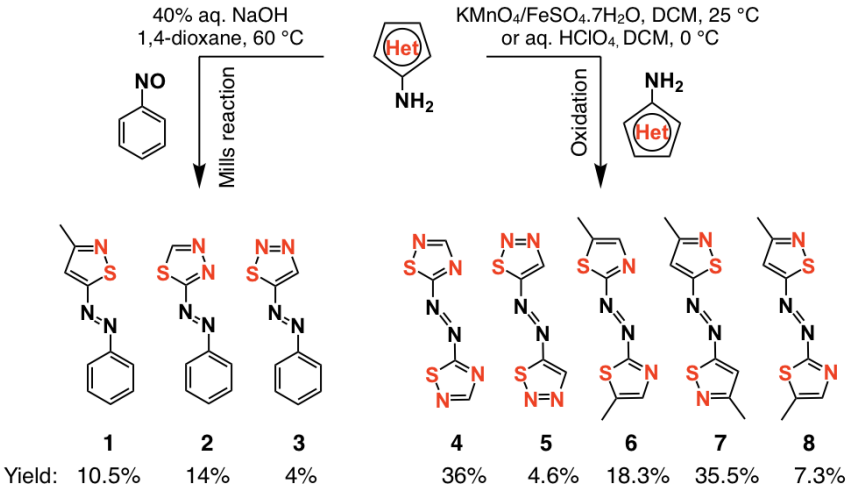

Scheme 1: Synthesis of photoswitches from amino-heteroaryl derivatives via Mills reaction with nitrosobenzene (**1**–**3**) or oxidation (**4**–**8**).

DFT calculation to get an insight to their light absorption (λ_{max}) properties (Table S1). Based on the calculated λ_{max} values, we selected eight compounds for synthesis, including those photoswitches with the longest and third longest λ_{max} (Table S1, Entries **k** and **x**). We used a general one-step procedure for the synthesis of compounds **1**–**8** (Scheme 1). Compounds **1**–**3** were synthesized via Mill`s reaction using the corresponding 2-amino heteroarene derivatives and nitrosobenzene (Scheme S1). Compounds **4**–**7** were synthesized by homo-oxidation of the corresponding 2-amino heteroarene derivatives (Scheme S2). Although azobisthiazole showed the second longest λ_{max} by calculation (440 nm, Table S1, Entry **j**), the oxidation of 2-amino thiazole did not give the target compound, probably due to the undesired oxidation at S atom of thiazole. However, a methyl substituent at position 5 of the amino thiazole gave azobis(methylthiazole) (compound **6**) in 18% yield. This compound can also be synthesized by a multiple-step reaction as appeared in a recent thesis report.[26] The asymmetric heteroaryl azo compound **8** was synthesized by oxidizing 2-amino-3-methylthiazole and 5-amino-3-methylisothiazole, yielding 7.3% along with corresponding symmetric heteroaryl azo compounds (Scheme S2). The NMR, Mass and X-ray analysis confirmed the structures of target compounds **1**–**8** (Figure S1-S24, Figure 3).

Photophysical studies

We then studied the absorption maximum of the **1**–**8** photoswitches (Figure 1, 2a). As estimated from the DFT-calculated λ_{max} values, the experimental λ_{max} of compounds **1**–**8** varied depending on the type of aryl moieties. The absorption spectra of these photoswitches exhibited a strong absorption band (λ_{max} = 332–429 nm) assignable to π-π^* electron transition bands. Figure 2b demonstrates the correlation between calculated and experimental λ_{max} values. Compounds **1**–**8** exhibited a clear positive correlation between calculated and experimental values, with the smallest calculated λ_{max} corresponding to the smallest experimental λ_{max}, and similarly for the largest values. This method showed a consistent trend across the compounds, demonstrating its reliability in theoretical predictions.

Upon light irradiation at suitable wavelength (365, 405, 430, 450 or 470 nm), a change in the absorption bands was observed, indicating that the photoswitches isomerized from *trans* isomer to *cis* isomer (black curves; before irradiation, and red curves; after irradiation) (Figures 1 and S25). The reverse isomerization occurred either thermally or by irradiating a longer wavelength light (430, 470, 525 or 568 nm. blue curves; after irradiation) (Figures 1 and S26). The composition of *trans* and *cis* isomers at the photostationary state (PSS) at various wavelengths was determined either from ^{1}H NMR (compounds **1**, **2**, **3** and **7**) or from absorption spectra (compounds **4**, **5**, **6** and **8**) (Figures 2a, S27–S30). Compounds **7** and **8**, having the isothiazole group, showed efficient photoisomerization under longer wavelength visible light irradiation, with large composition shift between *trans*-rich and *cis*-rich PSSs. For example, compound **7** achieved 81% *cis* at PSS with 405 nm light and 74% *trans* at PSS with 470 nm light. Compound **8** isomerized efficiently from *trans* to *cis* under various visible light irradiation achieving >73% *cis* isomer at PSS with 430 nm light, >66% *cis* at PSS with 450 nm, and >47% *cis* at PSS with 470 nm. Under 525 nm light, compound **8** gave >83% *trans* isomer at PSS (Figure 2a).

Assuming the compounds followed first-order thermal isomerization kinetics, the half-lives ($t_{1/2}$) of *cis* isomers were studied by monitoring the change in absorbance at the λ_{max} after *cis*-rich PSS. (Figures 2a, S31–S36). The $t_{1/2}$ values vary from several seconds to tens of hours. Compound **1** showed the longest half-life ($t_{1/2}$ = 45.2 h) among the 8 compounds studied. Compounds **4** and **6** exhibited relatively short half-lives of their *cis*-isomers, so brief that their changes could not be accurately tracked by a conventional spectrophotometer. It was estimated that they have half-lives of approximately several seconds. Compound **7** and **8** showed half-lives of 2.9 hours (λ_{max} = 338 nm) and 2.7 min (λ_{max} = 399 nm), respectively. The *cis*-life time of these photoswitches was decreased with increase in λ_{max}, a

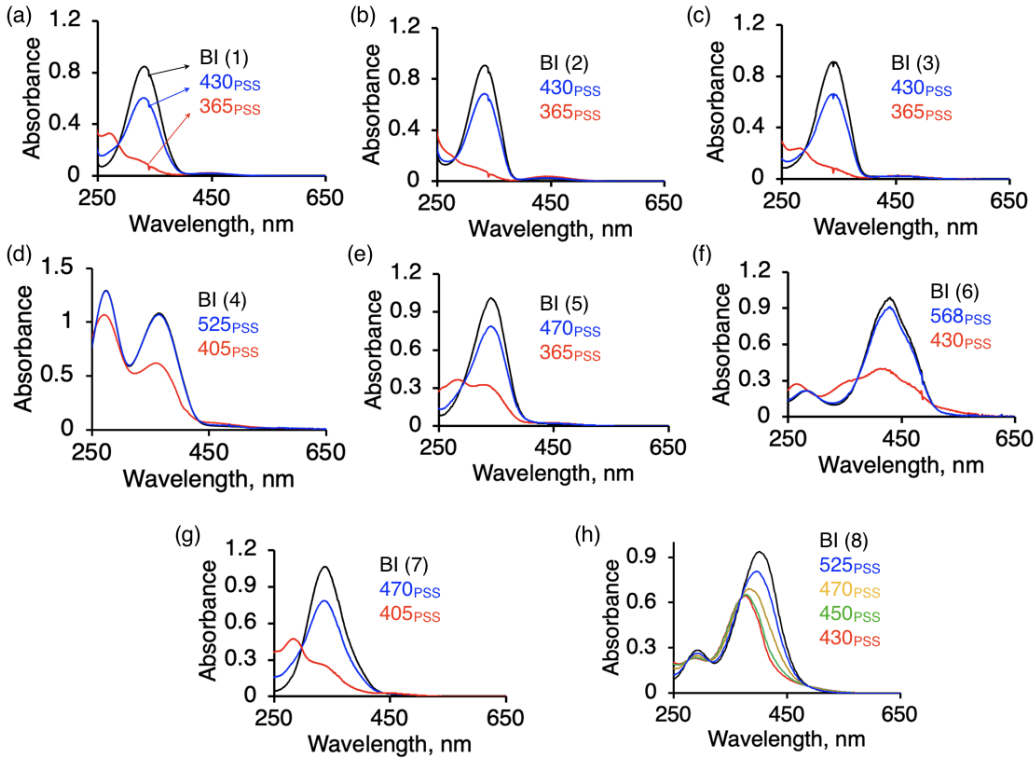

Figure 1: (a–h) UV–visible absorption spectra of **1**–**8** in acetonitrile at 25 °C before irradiation (BI, black lines) and at the *cis*-rich PSS under 365, 405 or 430 nm irradiations (365_{PSS}, 405_{PSS}, 430_{PSS}; red lines) and at *trans*-rich PSS under 430, 470, 525 or 568 nm irradiations (430_{pss}, 470_{PSS}, 525_{PSS}, 568_{PSS}; blue lines). In (h), intermediate PSSs under 450 and 470 nm are added (450_{PSS} and 470_{PSS}; green and yellow lines, respectively).

similar tendency seen in the substituted azobenzenes like 4-aminoazobenzene.[27,28]

Structural aspects of photoswitches in *trans* and *cis* isomers

To understand the molecular structure of the photoswitches, single X-ray crystallography was performed. Single crystals of the *trans* isomers (compounds **2**–**6 and 8**) and *cis* isomers (compounds **2** and **3**) were obtained using the vapor diffusion method in a chloroform-hexane solvent system, maintained at low temperature for 2 days. A planar geometry was observed in the *trans* isomers of compounds **2**, **3**, **4**, **5**, **6** and **8**, similar to the azobenzene molecule[29], where the phenyl, azo, and heteroaryl moieties all lie in the same plane (Figure 3 a-f). Unlike the typically observed twisted geometry of the *cis* isomer of azobenzene, the *cis* isomer of compound **3**, which contains a 1,2,3-thiadiazole group, displayed an orthogonal geometry. In this isomer, the phenyl and thiadiazole rings are oriented perpendicularly with the sulfur atom of the thiadiazole ring facing the phenyl ring (Figure 3b). This configuration is similar to that observed in our previously reported phenylazothiazole photoswitch.[16] In the case of compound **2**, with a 1,3,4-thiadiazole ring, the phenyl and thiadiazole rings are in face-to-face orientation (Figure 3a). Additionally, time-dependent density-functional theory (TDDFT) calculations were carried out in acetonitrile medium to analyse the molecular structure (Figure 3g-j). The *trans* isomers of compounds **2**–**5** showed planar geometries with phenyl, azo and thiadiazole moieties in the same plane. The *cis* isomers of compounds adopted twisted

(a)

Photo-switches	(π-π^*) (*E*)	(π-π^*) (*E*)	(n-π^*) (*E*)	(n-π^*) (*Z*)	Conversion (%)		$t_{1/2}$
	$\lambda_{max\ cal.}$	λ_{max}	λ_{max}	λ_{max}	*E*–*Z*	*Z*–*E*	(h, 25 °C)
1	377	332	448	448	94 (365 nm)	61 (430 nm)	45.2
2	366	334	448	448	90 (365 nm)	87 (430 nm)	29.4
3	377	345	453	458	93 (365 nm)	74 (430 nm)	24.3
4	404	362	483	484	>58 (405 nm)	>95 (525 nm)	-
5	427	343	450	450	>70 (365 nm)	>77 (470 nm)	3 min
6	459	429	-	535	>70 (430 nm)	>93 (568 nm)	-
7	404	338	463	460	81 (405 nm)	74 (470 nm)	2.9
8	431	399	-	-	>73 (430 nm) >66 (450 nm) >47 (470 nm)	>83 (525 nm)	2.7 min

(b)

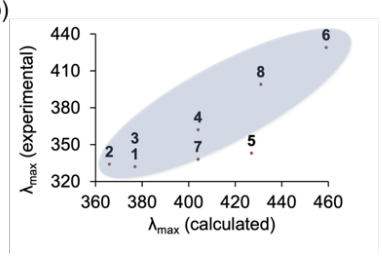

Figure 2: (a) Selected photophysical parameters of photoswitches **1**–**8**. (b) Relationship between experimental and calculated λ_{max}. A grey shadow indicates a positive correlation between them.

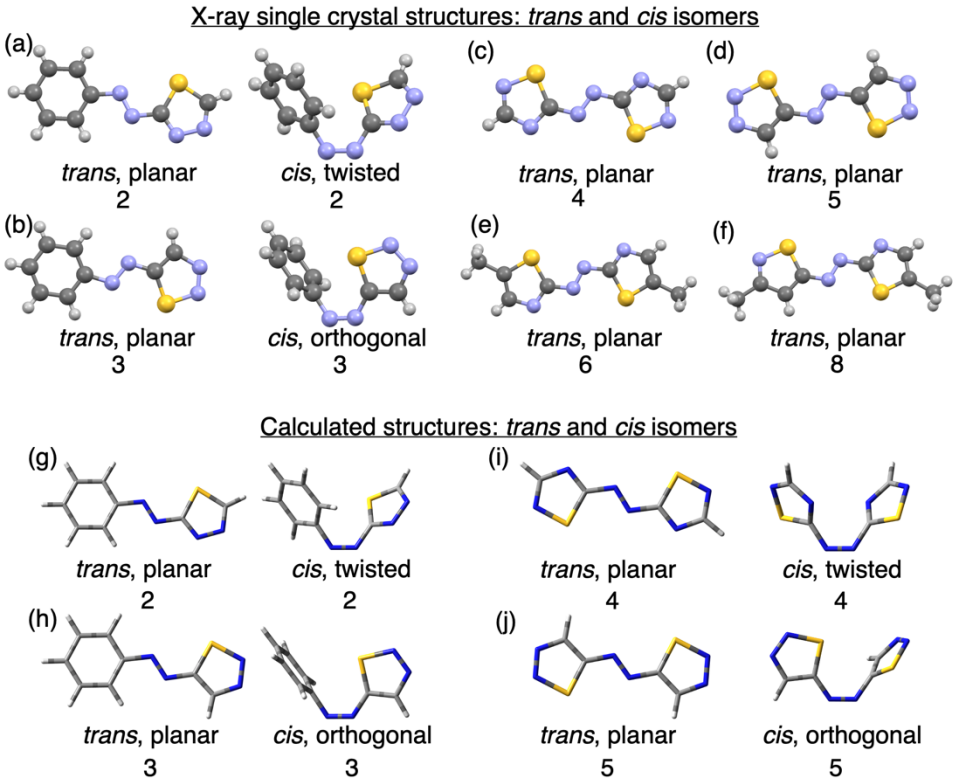

Fig. 3: (a–f) Single-crystal X-ray structures of both *trans* and *cis* isomers of **2** and **3**, and the *trans* isomers of **4**–**6, 8**, (g-j) Geometry optimized calculated conformations of both *trans* and *cis* isomers of **2**–**5**. (gray = C; light gray = H; purple = N; gold = S).

and orthogonal conformations as seen in the X-ray crystal structure of compound **2** and **3**, respectively. The theoretical calculations of molecular structures match the X-ray crystallography results, confirming their reliability in predicting the molecular geometry of the designed molecules.

Conclusions

In conclusion, we have synthesized novel azophotoswitches with various five-membered heteroaryl groups such as thiazole, isothiazole, thiadiazole and isothiadiazole. These compounds were designed with heteroaryl units on either one or both sides of the azo bond. DFT calculations were used to predict the λ_{max} values of 24 compounds, resulting in the selection of eight compounds for study, including those with the longest λ_{max}. Compound **8** containing thiazole and isothiazole moieties, showed longer λ_{max} than any of the synthesized compounds. The λ_{max} of the photoswitch shifted to longer wavelength with decrease in *cis*-life time, as seen in substituted azobenzenes. It efficiently isomerized under visible light at 430 nm, 450 nm, 470 nm (*trans* – *cis*) and 525 nm (*cis* – *trans*). X-ray crystallography showed that the *trans* isomers displayed a planar geometry, while the *cis* isomer of compound **3** adopted a unique orthogonal conformation. The calculations employed in the study reliably predicted both the absorbance maximum and molecular geometry. This work will expand the range of visible-light active photoswitches design, facilitating advancements in photopharmacology.

Experimental

General procedure for synthesis of compounds 1-3.

To a warm (40 °C) NaOH solution (40% aq., 1 mL), 2-amino heteroaryl compounds (2.3 mmol) in 1,4-dioxane (2.5 mL) was added and gently heated to 60 °C. Then, nitroso-benzene (2.53 mmol) was added slowly, and the mixture was stirred for 2 hours. The reaction mixture was then cooled and quenched with water and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The target compound was then isolated by column chromatography.

General procedures for synthesis of compounds 4-8.

(1) To cold sodium hypochlorite solution, cool suspension of aminothiadiazole (4.9 mmol) in dichloromethane (15 mL) was added little by little followed by stirring for 1 hour at 0 ˚C. The reaction mixture was quenched with water and extracted with dichloromethane (3 x 25 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The target compound was then isolated by column chromatography.

(2) A heteroaryl amino compound (5 mmol) was dissolved in dichloromethane. Potassium permanganate (15 mmol) and

ferrous sulfate heptahydrate (10 mmol) were ground together until homogenous. The resulting powder was added to the dichloromethane solution. The mixture was stirred for 24 hours at room temperature. Afterward, the reaction mixture was filtered through celite, and the solvent evaporated. Finally, the target compound was isolated using column chromatography.

Measurement of thermal half-life

A freshly prepared solution was irradiated at 365 nm, or 405 or 430 nm until its photostationary states and immediately kept for thermal back *Z–E* isomerization in dark at 25 °C. In all cases, 6–8 spectra at fixed time intervals were recorded under dark condition to minimize the effect of light beam on thermal back isomerization. Then, a first order rate constant (*k*) for the thermal back *Z–E* isomerization reaction was obtained using the equation.

$$ln\frac{A_t}{A_0} = ln\frac{Abs(BI) - Abs(time)}{Abs(BI) - Abs(PSS)} = -kt$$

Abs(BI) = absorbance at initial state at λ_{max}.
Abs(PSS) = absorbance at photostationary state at λ_{max}.
Abs(time) = absorbance at λ_{max} at different time interval for thermal back isomerization.
For a first order reaction, half-life ($t_{1/2}$) can be calculated using the equation:

$$t_{1/2} = 0.693/k$$

Single crystal X-ray Crystallography

General procedure for the crystallization of compounds 2, 3, 4, 5, 6 and 8

A small vial containing the compound dissolved in chloroform (10 mmol, 200 μL) is placed inside a larger container with hexane (70 mL). The system is maintained at -20 °C for 2 days, ensuring it is well-sealed to prevent solvent evaporation. During this time, the concentration of hexane in the vial increases, causing the solubility of the compound in the solvent to gradually decrease, leading to the slow precipitation of crystals from the solution.

Crystallization of *cis* isomer of compounds 2 and 3

The compound solution in a small vial was irradiated with 365 nm light until it reached the photostationary state. Subsequently, the small vial was immediately transferred to a larger container containing hexane and allowed to crystallize, following the general procedure.

Cryoloop was used to mount the single crystals. Crystallographic data was collected using a Rigaku XtaLab Synergy diffractometer with a single microfocus Mo Kα X-ray radiation source (PhotonJet-S), equipped with a Hybrid Pixel (HyPix) Array detector (HyPix-6000HE). Data collection, cell refinement, and data reduction were carried out with CrysalisPRO (Rigaku Oxford Diffraction, 2017). The initial structure was solved by SHELXT and expanded using Fourier techniques and refined on F2 by the full-matrix least-squares method SHELXL2018/3 package compiled into OLEX2 package. All parameters were refined using anisotropic temperature factors, except for hydrogen atoms, which were refined using the riding model, with a fixed C–H bond distance.

DFT calculation

Theoretical calculations were performed using Gaussian 09 (Revision D.01). GaussView 6.0 was used to draw and visualize the molecular structures and to feed the inputs. Density functional theory (DFT) and time dependent density functional theory (TDDFT) were employed to optimize the geometries and to obtain the electronic transition in the ground state, respectively. The 6-31+G(d,p) basis set with Becke's three-parameter hybrid exchange and the Lee-Yang-Parr's correlation functional (B3LYP) was used for geometry optimization. The solvent stabilization of different isomers was incorporated by considering integral equation formalism-polarizable continuum model (IEF-PCM) and choosing acetonitrile as medium.

Author Contributions

N.M.C. conducted most of the experiments and data analysis. N.T. conceptualized the project and P.K.H. helped in the synthesis and data analysis. S. S. performed DFT calculations. K. T. and T. N. measured X-ray crystal structure. H. M., and K. I. discussed on the results, N.T. supervised, and all authors contributed to writing the manuscript.

Conflicts of interest

"There are no conflicts to declare".

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