HOKKAIDO UNIVERSITY

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Author(s)	Madappuram Cheruthu, Nusaiba
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Abstract of Doctoral Dissertation

Degree requested: Doctor of Soft Matter Science

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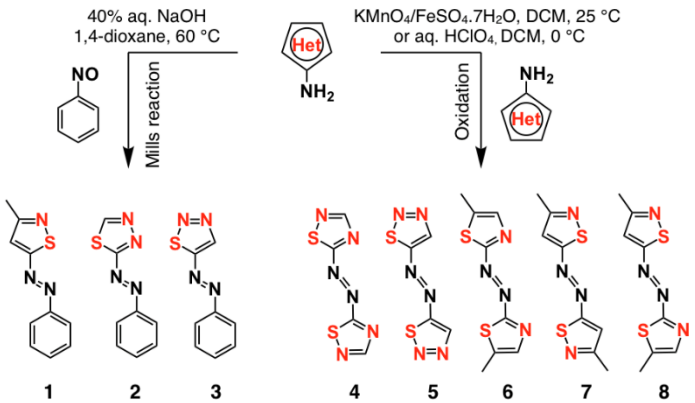
Title of Doctoral Dissertation

Study on Azophotoswitches containing thiazole, isothiazole, thiadiazole and isothiadiazole
(チアゾール、イソチアゾール、チアジアゾール、イソチアジアゾールを含むアゾフォトスイッチに関する研究)

Photoswitches are compounds capable of existing in two isomeric forms, which can be reversibly switched by light irradiation. These molecules have been widely used in material and biological sciences.[1,2] A distinct category is azophotoswitches that contain an "azoaryl" segment. A typical example is azobenzene, which undergoes *trans* to *cis* photoisomerization by 365-nm UV light and reverse isomerization either thermally or photochemically. Visible light-responsive azophotoswitches are essential for various applications, particularly in biology, as UV light poses risks of tissue damage and poor tissue penetration. Azophotoswitches having 5-membered heteroaryl units like pyrrole, pyrazole, imidazole, isoxazole and triazole have attracted interest because of their distinct light absorption and photoisomerization characteristics.[3] However, these azophotoswitches typically require UV light for their isomerization. In contrast, recent studies from our lab found that the azophotoswitches containing "thiazole" unit can isomerize by visible light (405 nm) without compromising their photophysical properties.[4] Aiming for expanding the visible light azophotoswitches, my Ph.D. research focused on designing novel photoswitches with unexplored 5-membered heteroaryl units like isothiazole, thiadiazole, and isothiadiazole. I initially screened 24 azophotoswitches using DFT calculations to identify compounds with maximum absorption (λ_{max}) at longer wavelengths and then synthesized eight selected azophotoswitches, and investigated their photophysical as well as structural charesteristics.

Compounds **1**–**8** were synthesized by a general one-step Mills reaction using 2-amino heteroarene derivatives and nitrosobenzene (**1**–**3**), or by homo-oxidation of 2-amino heteroarene derivatives (**4**–**7**) (Scheme 1). The structures of compounds **1**–**8** were confirmed by NMR spectroscopy, mass spectrometry, and X-ray analyses. The absorption spectra of these photoswitches exhibited a strong absorption band (λ_{max} = 332–429 nm) assignable to π–π* electron transition bands. Compounds **1**–**8** exhibited a clear positive correlation between the calculated and experimental values, with the smallest calculated λ_{max} value corresponding to the smallest experimental λ_{max} value, and similarly for the largest values (Figure 1b). Upon light irradiation at suitable wavelengths (365, 405, 430, 450 or 470 nm), a change in the absorption bands was observed, indicating that the photoswitches isomerized from the *trans* isomer to the *cis* isomer. The reverse isomerization occurred either thermally or upon irradiating a longer wavelength light (430, 470, 525 or 568 nm) (Figure 1a). Among the azophotoswitches developed in this study, compound **8** containg both thiazole and isothiazole



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

group, isomerized efficiently from the *trans* to *cis* isomer under visible light irradiation at various wavelengths, achieving >73% *cis* isomer in the PSS with 430 nm light, >66% *cis* isomer in the PSS with 450 nm, and >47% *cis* isomer in the PSS with 470 nm. Under 525 nm light, compound **8** gave >83% *trans* isomer in the PSS. I also studied the half-lives ($t_{1/2}$) of *cis* isomers by monitoring the change in absorbance at λ_{max} after the *cis*-rich PSS and found that the $t_{1/2}$ decreased with an increase in λ_{max}, a tendency similar to that seen in substituted azobenzenes.[5] To understand the molecular structures of the photoswitches, single X-ray crystallography was performed. A planar geometry was observed in the *trans* isomers of compounds **2**, **3**, **4**, **5**, **6** and **8**, similar to the azobenzene, where the phenyl, azo, and heteroaryl moieties all lie in the same plane. 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 a unique orthogonal geometry. Here, the phenyl and thiadiazole rings are oriented perpendicularly with the sulfur atom of the thiadiazole ring facing the phenyl ring.

(a)

Photo-switches	(π-π^*) (*E*)	(π-π^*) (*E*)	(n-π^*) (*E*)	Conversion (%)		$t_{1/2}$
	λ_{max} cal.	λ_{max}	λ_{max}	*E*–*Z*	*Z*–*E*	(h, 25 °C)
1	377	332	447	94 (365 nm)	61 (430 nm)	45.2
2	366	334	448	90 (365 nm)	87 (430 nm)	29.4
3	377	345	448	93 (365 nm)	74 (430 nm)	24.3
4	404	362	483	>58 (405 nm)	>95 (525 nm)	-
5	427	343	450	>70 (365 nm)	>77 (470 nm)	3 min
6	459	429	-	>70 (430 nm)	>93 (568 nm)	-
7	404	338	477	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)

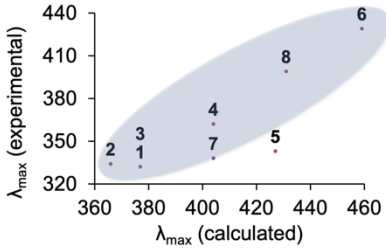


Figure 1: Selected photophysical parameters of compounds **1**–**8** (a) and the plot showing the general tendency of experimental and calculated λ_{max} (b).

Finally, this study has clearly shown that the calculated data (both λ_{max} and molecular geometry) closely matches the experimental results, confirming the accuracy of the theoretical models in predicting novel visible-light azophotoswitches and determining their molecular geometries. This study also reveal that the incorporation of isothiazole and thiazole groups in azophotoswitches results in a redshift of λ_{max} to longer wavelengths, enabling efficient isomerization under visible light. This work broadens the scope of visible-light-active photoswitch design for the advancements in photopharmacology and related applications.[6,7]

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