



# 6th International Electronic Conference on Medicinal Chemistry

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## The analysis of photochemical anti-syn isomerization process across the $-N=N-$ bond in heterocyclic imines

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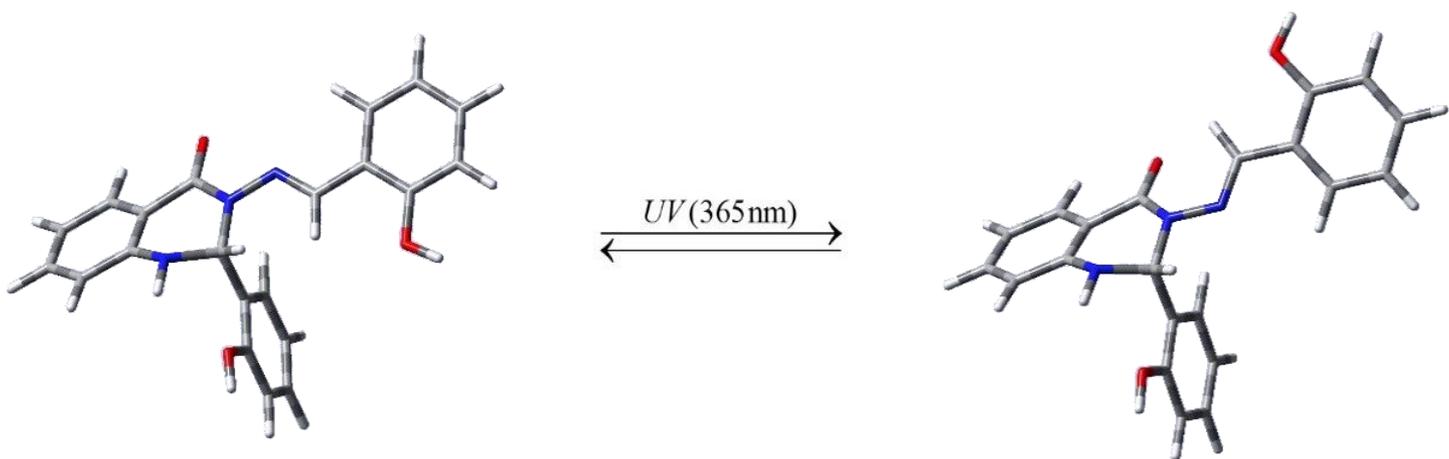
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# The analysis of photochemical anti-syn isomerization process across the $-N=N-$ bond in heterocyclic imines



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**Abstract:** Many biologically active molecules experience photoisomerization processes after light-induced excitation (e.g. rhodopsin). Important photochemical properties showed particularly compounds possessing aromatic systems in the presence of conjugated heteroatoms. Such systems often constitute a part of natural biomolecules and play a crucial role in essential biochemical and biological processes. Due to photochemical nature of these aromatic compounds, such as Schiff bases, they are often studied for pharmacological applications and used in biochemistry and medicine. For this reason, we focused our study on photochemical processes of quinazolinone-based Schiff bases. The isomerization from the energetically more favourable anti-isomer to the syn-isomer by UV/vis excitation has been found namely in the systems possessing a double bond systems. Presented analysis deals with NMR spectroscopy and theoretical DFT analysis of photochemical processes of the Schiff base possessing a quinazolinone moiety with a series of model compounds to investigate the photochemical behaviour of the  $-N=N=$  linkage. The NMR experiments in solution showed that irradiation at 365 nm leads to photochemically-induced isomerization from the anti- to the higher-energy syn-form around the  $-N=N=$  linkage.

**Keywords:** NMR; Photoactive biomolecules; Photoisomerization; Schiff-bases



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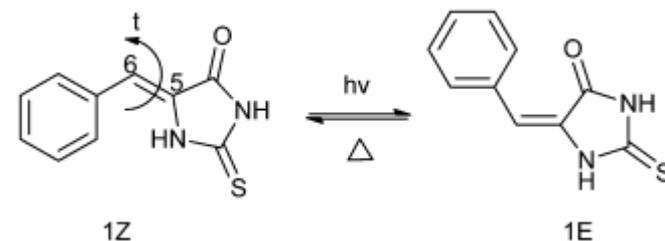
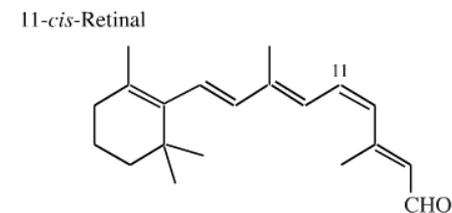
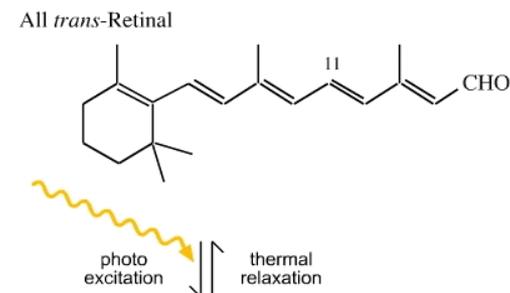
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# Introduction

- some chemical substances are photoactive when subjected to UV radiation
- can form many reactive species
- play a crucial role in essential biochemical processes
- exhibit structural changes and biological activities upon radiation
- act as the first step in a number of light-induced biological processes
- photochemical nature makes them applicable in many fields



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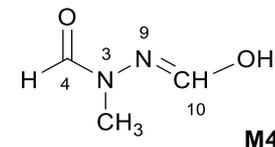
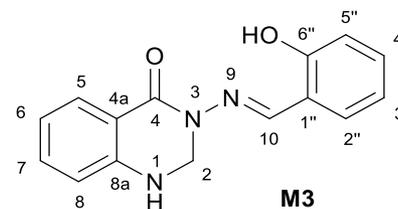
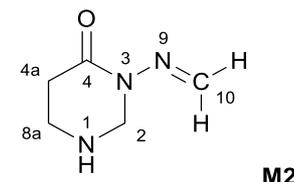
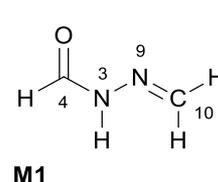
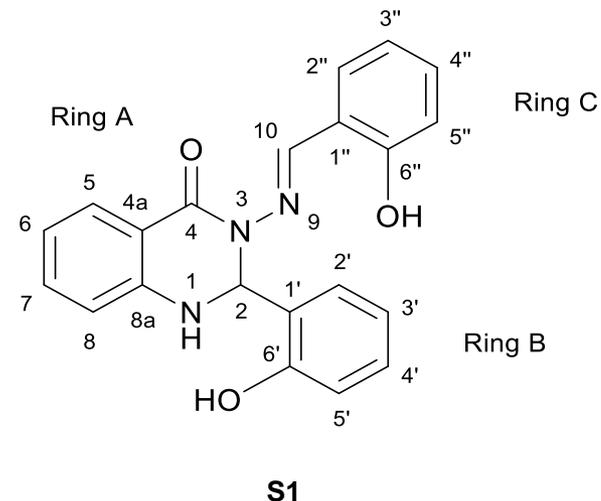
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# Compounds

- Schiff-base possessing a quinazolinone moiety (**S1**)
- model compounds (**M1-M4**) possessing N=N=CH moiety
- significance of Schiff bases can be attributed to the presence of the N=C or N=N double bond
- the –N–N=CH– array of atoms has different photochemical properties compared to the N=N double bond



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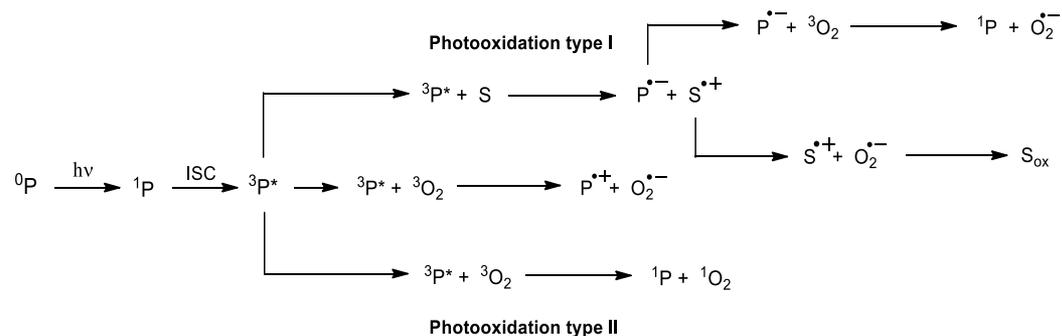
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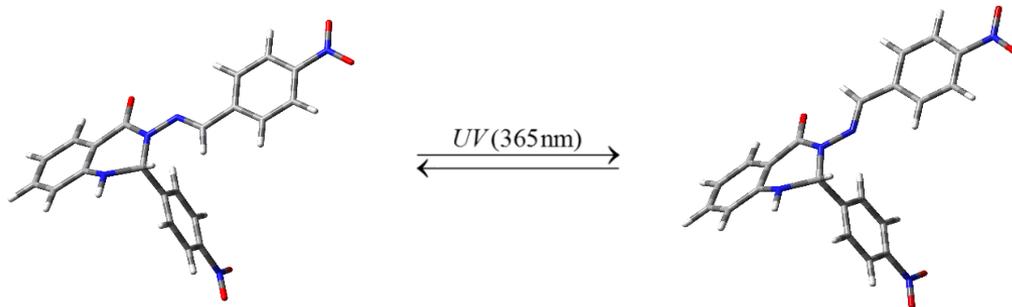
# Outline

- study of photochemical behaviour
  - generation of ROS via photosystem I/II mechanism
  - structural changes upon irradiation



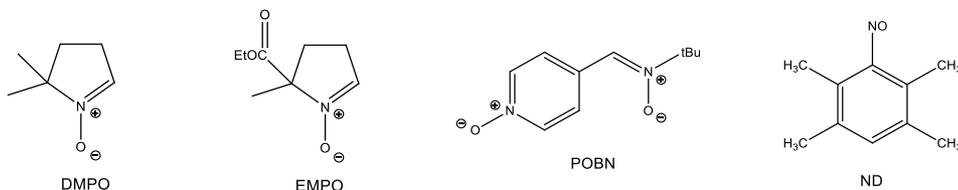
P = photosensitizer, S = substrate, <sup>0</sup> = ground state, <sup>1</sup> = singlet, <sup>3</sup> = triplet, \* = activated state, ISC = intersystem crossing

- spectroscopic characterisation
  - EPR (X-band)
  - NMR (1D and 2D)
- DFT calculations
  - geometry optimisation
  - excited states study

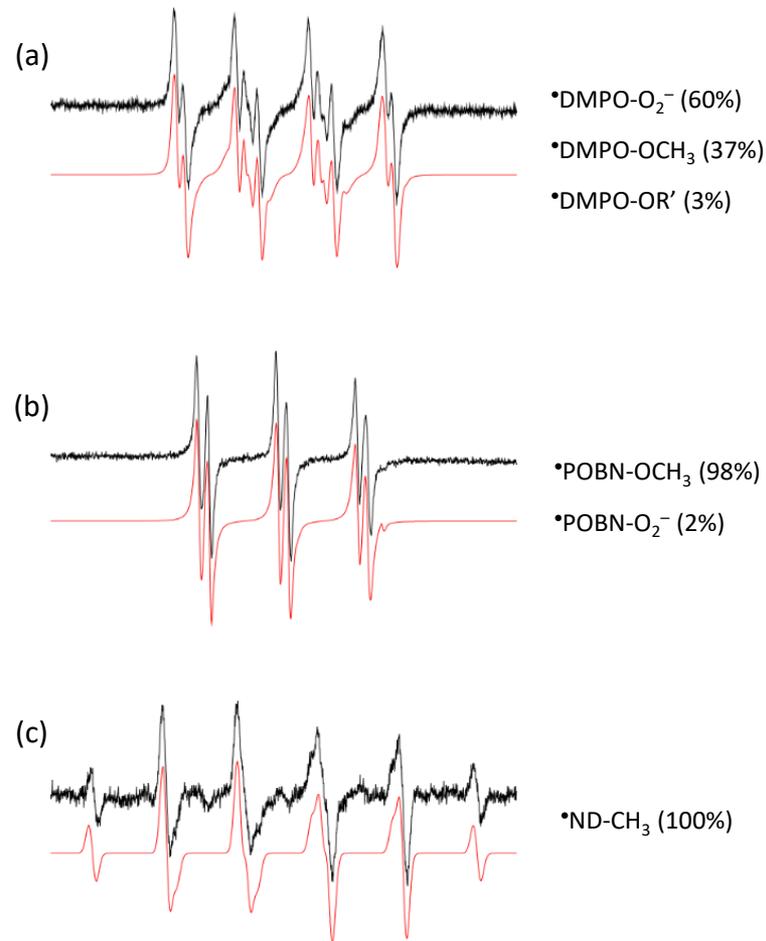
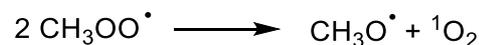
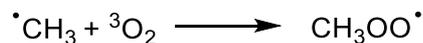


# Results and discussion

- DMSO solvent, RT, continuous irradiation at 365 nm
- spin-trapping technique, spin traps used



- detected oxygen centred adducts, namely  $\bullet$ DMPO- $O_2^-$  (a-c) and carbon centred adduct  $\bullet$ ND- $CH_3$  (d)
- reactive species are formed via consecutive reactions in DMSO under atmospheric conditions



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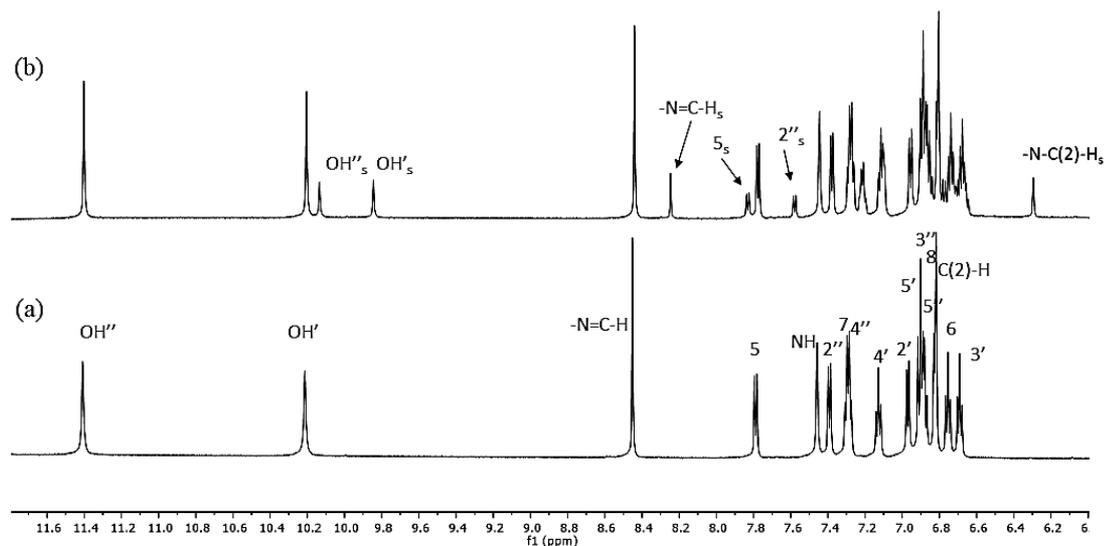
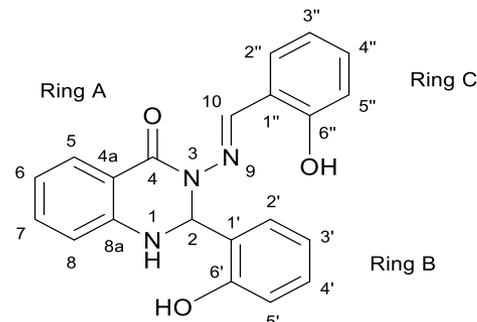
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# Results and discussion

- 600 MHz, RT, DMSO, before irradiation (a)
- new resonances originating from the *syn*-isomer after 10 min irradiation at 365 nm (b)
- intensities had been increasing with irradiation
- isomerization varied in a manner correlated to the structure
- stabilisation of *syn*-isomer via H-bonds



High-resolution 600 MHz  $^1\text{H}$  NMR spectrum of **51** in DMSO at 25°C before irradiation (a) and after 10 minutes of UV irradiation ( $\lambda_{\text{max}} = 365$  nm) (b). Smaller signals (marked with subscript s) belong to the *syn*-isomer, which formed upon irradiation; assignments without indices belong to the main form (*anti*-isomer).

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# Results and discussion

- temperature coefficients of the  $-N_3-N=C(H)$  protons and OH protons (Table 1)
- coefficients for the OH protons for **1** – **7** varied between -5.36 and -6.11 ppb/K
- OH groups are involved in intramolecular H-bonds with different strengths depending upon the structure and conformation
- the same behaviour also for the NH protons
- stability of *syn*-isomers due to the formation of intramolecular hydrogen bonds

**Table 1.** Temperature dependence of the chemical shifts of  $-N=C(H)$  and  $-OH$  protons in **S1**.

		(20°C)	(25°C)	(35°C)	(45°C)	(55°C)	(65°C)	ppb/K
<b>S1</b>	<i>anti</i> -OH'	10.233	10.203	10.142	10.080	10.020	9.958	-6.11
	<i>anti</i> -OH''	11.434	11.409	11.353	11.299	11.246	11.193	-5.36
	<i>anti</i> -N <sub>3</sub> -N=CH	8.441	8.454	8.477	8.499	8.522	8.542	-2.24
	<i>anti</i> -NH	7.484	7.460	7.408	7.357	7.305	7.254	-5.11

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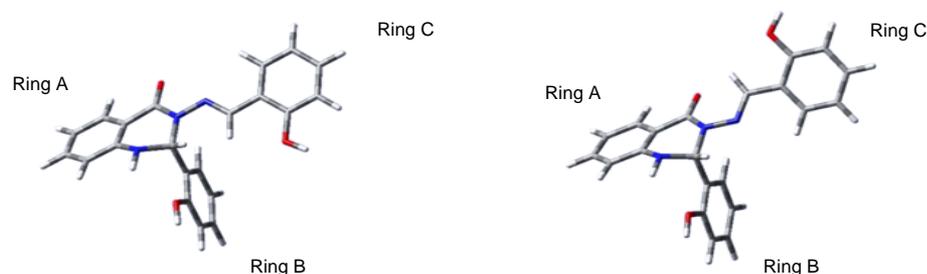
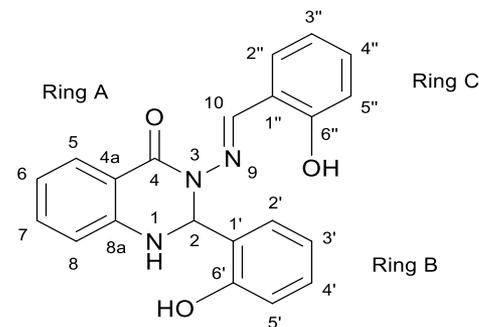
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# Results and discussion

- The relative energies between the *anti*- and *syn*-forms for **M1-M4** and **S1** are listed in Table 2 and the selected geometry parameters are in Table 3 (next slide).
- the N<sub>3</sub>-N<sub>9</sub> bond has partial double-bond character (around 1.37 Å, see Table 3, row 3)
- incorporation of the heterocyclic moiety (**M2**) to the structure of **M1** caused the bond elongation of the bond (1.380 vs. 1.356 Å).
- A significant effect is also seen after addition of the aromatic ring C to the carbon atom C<sub>10</sub>; there is a visible zigzag double-bond formation in the C<sub>4</sub>-N<sub>3</sub>-N<sub>9</sub>-C<sub>10</sub> linkage, where the N<sub>3</sub>-N<sub>9</sub> bond was shortened and the N<sub>9</sub>-C<sub>10</sub> bond was prolonged (Table 3, rows 3 and 4)



DFT-optimised geometries of compound **S1**: *anti*-isomer (left) , *syn*-isomer (right)

**Table 2.** DFT-computed energy differences (*kJ/mol*) between the *anti* and *syn*-forms for all compounds using  $\omega$ B97XD functional, 6-311++G(2d,2p) basis set and SMD solvent model (DMSO)

Compound	<b>M1</b>	<b>M2</b>	<b>M3</b>	<b>M4</b>	<b>S1</b>
$\Delta E_{syn} - \Delta E_{anti}$	7.88	6.09	4.99	2.39	7.56

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# Results and discussion

**Table 3.** Selected optimised bond lengths (Å), bond angles (degrees) and torsion angles (degrees) for **M1–M4** and **S1** obtained by DFT calculations at the  $\omega$ B97XD/6-311++G(2d,2p) using SMD solvent model (DMSO)

	M1		M2		M3		M4		S1		
	<i>anti-</i>	<i>syn-</i>	<i>anti-</i>	<i>syn-</i>	<i>anti-</i>	<i>syn-</i>	<i>anti-</i>	<i>syn-</i>	<i>anti-</i>	<i>syn-</i>	
<b>Bond length</b>	C <sub>1</sub> '–C <sub>6</sub> '	–	–	–	–	1.410	1.409	–	–	1.410	1.410
	C <sub>10</sub> –C <sub>1</sub> '	–	–	–	–	1.458	1.453	–	–	1.457	1.453
	N <sub>3</sub> –N <sub>9</sub>	1.365	1.371	1.365	1.375	1.357	1.387	1.374	1.402	1.360	1.386
	C <sub>10</sub> –N <sub>9</sub>	1.267	1.272	1.270	1.272	1.278	1.280	1.265	1.268	1.278	1.279
	C <sub>4</sub> –N <sub>3</sub>	1.356	1.356	1.380	1.368	1.385	1.385	1.358	1.349	1.388	1.384
	C <sub>2</sub> –N <sub>3</sub>	–	–	1.463	1.471	1.459	1.462	1.449	1.447	1.458	1.459
<b>Bond angle</b>	N <sub>3</sub> –N <sub>9</sub> –C <sub>10</sub>	120.7	116.5	120.1	123.1	122.7	117.5	118.6	113.4	122.5	117.9
	N <sub>9</sub> –C <sub>10</sub> –C <sub>1</sub> '	–	–	–	–	119.4	120.7	–	–	119.4	120.3
	C <sub>4</sub> –N <sub>3</sub> –C <sub>2</sub>	–	–	123.8	122.3	121.3	118.2	121.2	122.5	122.5	120.8
	C <sub>8a</sub> –N <sub>1</sub> –C <sub>2</sub>	–	–	110.4	109.8	116.7	115.2	–	–	116.8	116.3
	N <sub>1</sub> –C <sub>2</sub> –N <sub>3</sub>	–	–	110.4	110.2	109.0	108.0	–	–	108.2	107.4
	C <sub>4</sub> –N <sub>3</sub> –N <sub>9</sub>	121.6	130.8	115.8	126.5	114.9	119.8	117.1	120.8	115.0	120.6
	C <sub>1</sub> '–C <sub>2</sub> –N <sub>3</sub>	–	–	–	–	–	–	–	–	112.4	113.4
<b>Torsion angle</b>	C <sub>4</sub> –N <sub>3</sub> –N <sub>9</sub> –C <sub>10</sub>	–180	0	–170.9	14.8	–165.7	58.9	–180	–67.1	–167.3	57.4
	C <sub>2</sub> –N <sub>3</sub> –N <sub>9</sub> –C <sub>10</sub>	–	–	3.4	–177.7	–1.5	–156.8	0	131.1	1.3	–151.9
	N <sub>3</sub> –N <sub>9</sub> –C <sub>10</sub> –C <sub>1</sub> '	–	–	–	–	–179.5	–178.0	–	–	179.9	–178.1
	N <sub>9</sub> –C <sub>10</sub> –C <sub>1</sub> '–C <sub>6</sub>	–	–	–	–	–2.2	1.0	–	–	–2.3	2.0
	N <sub>3</sub> –C <sub>2</sub> –C <sub>1</sub> '–C <sub>2</sub> '	–	–	–	–	–	–	–	–	–9.3	–11.7
	N <sub>1</sub> –C <sub>2</sub> –N <sub>3</sub> –C <sub>4</sub>	–	–	–21.8	–31.1	–41.8	–53.6	–	–	–38.7	–48.1

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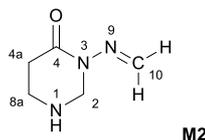
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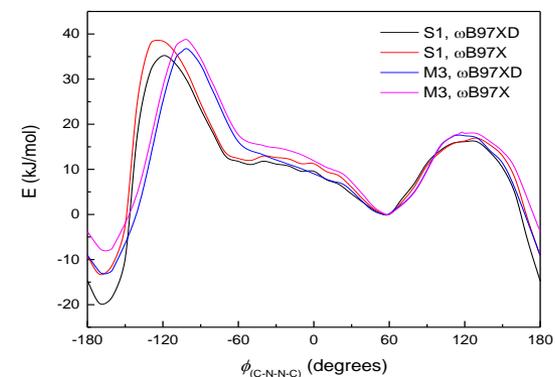
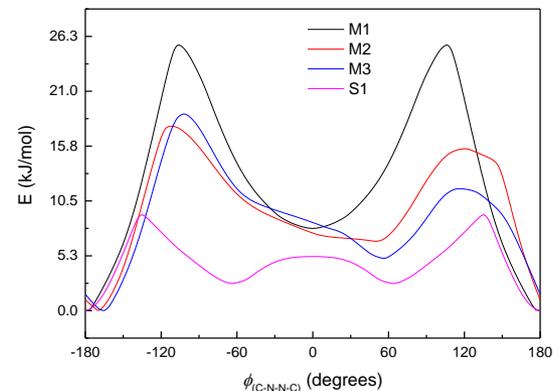
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# Results and discussion

- For **M1**, both the molecule and its energy profile with respect to  $D(C-N-N-C)$  are symmetric
- energy profiles of **S1** and **M1**, **M2** and **M3** are compared
- The  $C_4N_2$  ring present in **M2** introduces a major part of the asymmetry - steric repulsion between the Schiff's base  $CH_2$  group and the ring  $CH_2$  group



- The difference between **S1** and **M3** is the aromatic Ring B, which does not participate in the large  $\pi$ -system



Ground state energy curves ( $kJ/mol$ ) against  $C_4-N_3-N_9-C_{10}$  dihedral angle for **S1** and model systems. Top: energy profiles for **S1** and **M1**, **M2**, and **M3** (zeroed to lowest energy point on curve). Calculated at the  $\omega B97XD/6-311++G(2d,2p)$  level. Bottom: **S1** and **M3** (zeroed to *syn* minimum).

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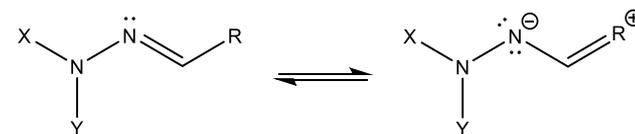
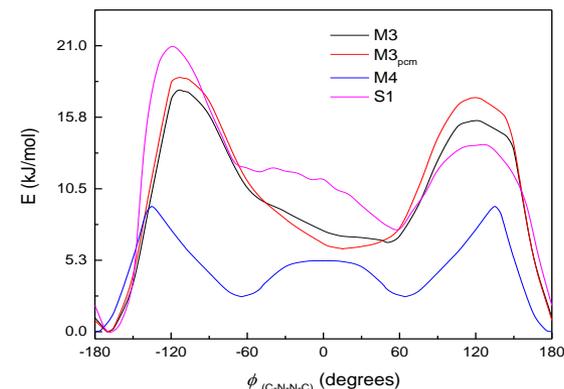
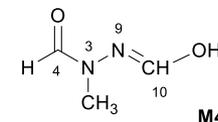
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# Results and discussion

- small shoulder around 0° in **S1**, **M2**, and **M3** is visible as a peak in the case of **M4**, less pronounced in case of **M2**
- steric repulsion between the C=O group and the electron pairs (two lone pairs, one N–C bond) on  $sp^3$ -hybridised N<sup>-</sup>
- This suggests that the peak (or shoulder) at 0° arises from resonance structures with negative charge at the Schiff's base nitrogen
- nearby electron-donating OH group shows such effects most strongly



Top: ground-state energy curves (in  $kJ/mol$ ) for **S1**, **M3**, **M4**, and **M3<sub>pcm</sub>** against  $D(C-N-N-C)$ . Bottom: resonance structure with negative charge on Schiff's-base nitrogen.

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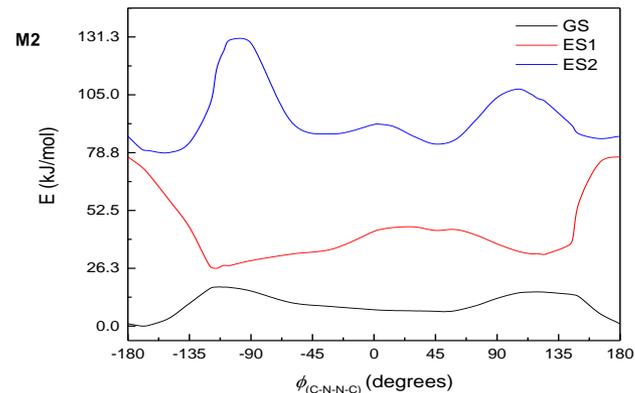
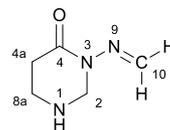
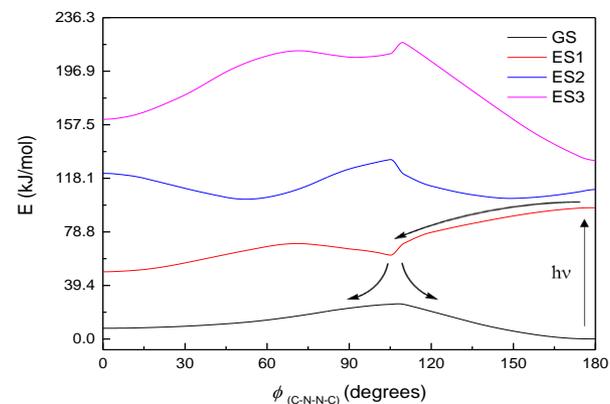
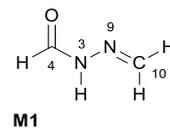
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# Results and discussion

- potential energy curves for ground and excited states against the dihedral angle  $D(\text{C-N-N-C})$ ; studied for all model compounds and **S1**
- first excited state has its highest energy at  $180^\circ$  and its lowest energy at  $0^\circ$
- The first state arises from an  $n-\pi^*$  excitation
- the dominant excitation is HOMO  $\rightarrow$  LUMO



Top: Energy curves for the ground state (GS) and first three excited states (ES1-ES3) of **M1**. Relative energies ( $\text{kJ/mol}$ ) of the states have been heavily adjusted for clarity.

Bottom: Ground state (GS) and first two excited states (ES1, ES2) energy curves for **M2**. Relative energies ( $\text{kJ/mol}$ ) of the curves have been adjusted for clarity.

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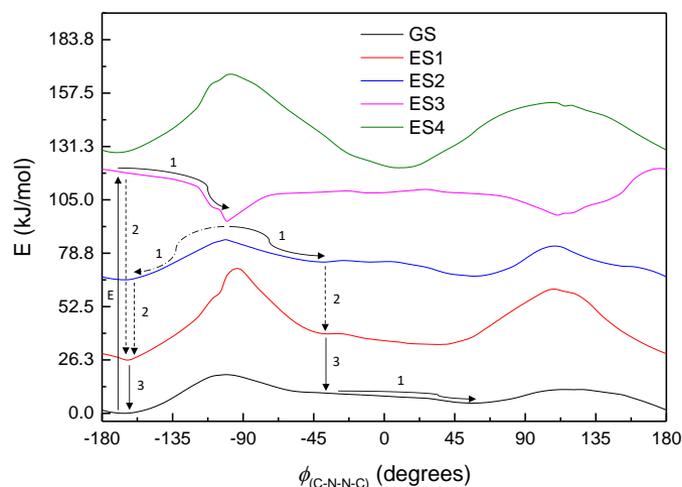
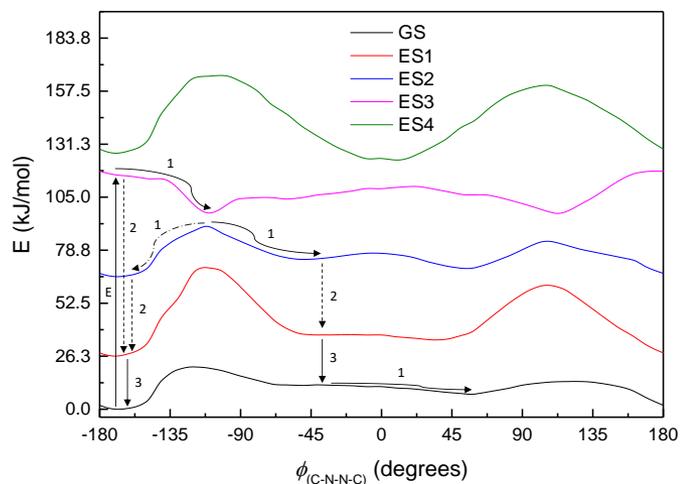
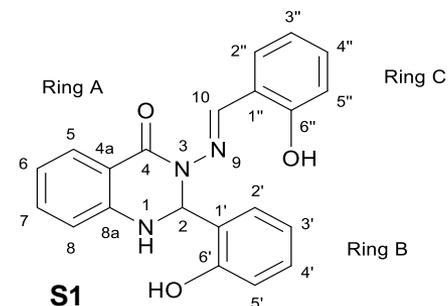
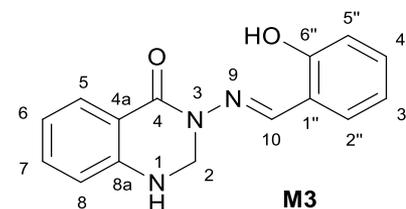
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# Results and discussion

- **M3** and **S1** – the situation is a little different
- the first two have similar energy profiles to the ground state; third is inverted
- the conical intersection between 2<sup>nd</sup> and 3<sup>rd</sup> excited state
- deexcitation mechanism is similar for both systems



Energy curves for ground state (GS) and excited states (ES1-ES4) of **M3** (left) and **S1** (right) with proposed mechanisms of excitation and deexcitation processes (E – excitation, 1 – structural relaxation, 2 – internal conversion, 3 – emission). Relative energies (kJ/mol) of the curves have been adjusted for clarity.

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# Conclusions

- EPR measurements evidenced the generation of ROS using spin-trapping technique
  - the presence of oxygen- and carbon-centred adducts
- NMR spectra proved the photoisomerization process around the N–N bond within the –N–N=CH– array
  - two isomers, *syn*-isomer formed, 25% of conversion
  - presence of hydrogen bonds
- DFT calculations
  - the *anti*-form to be lower in energy than the *syn*-form, in accordance with experiment
  - excited state energy curves; photoisomerization involves  $n-\pi^*$  excitations or proceeds purely via  $\pi-\pi^*$  states; the mechanism is determined by the  $\pi$ -system size
  - **M3** and **S1**, the 3<sup>rd</sup> singlet-singlet excitation ( $\pi-\pi^*$ ) results in an excited state with an appropriate energy profile for isomerisation; lower excitations are unlikely to be involved



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