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Synthesis, crystal structures and studies on Hg^{2+} sensing by the diazo derivatives of sulfathiazole and sulfamethoxazole

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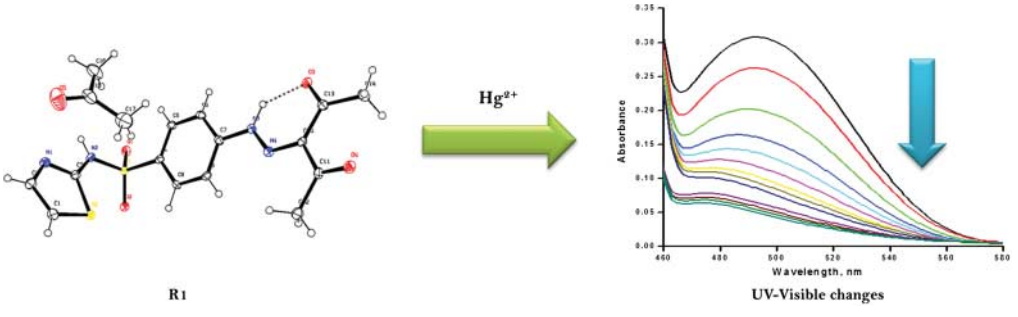
Diazocoupling of sulfathiazole and sulfamethoxazole with 2,4-pentanedione led to the syntheses of compounds **R1** and **R2**. These were fully characterized by single crystal X-ray diffraction studies in conjunction with UV–visible, IR, ^{1}H NMR, and mass spectral studies. Both the compounds were further screened for their possible use in metal ion recognition. Interestingly, compound **R1** showed a selective naked-eye response for Hg^{2+}, while **R2** did not give a color change for any metal ions. These results can be understood in terms of a solvent-assisted low-energy absorption band in **R1** that disappeared upon interaction with Hg^{2+}. This absorption band was not observed in the case of compound **R2** that consequently failed to show any naked-eye color change in the presence of metal ions.



Keywords: sulfa drug; 2, 4-pentanedione; diazo derivatives; crystal structure; Hg^{2+} sensing

1. Introduction

Cations are ubiquitous and play crucial roles in our ecosystem as well as in living systems (*1*). A variety of metal ions play pivotal roles in various metallo-enzymes. For example, Mn^{2+}, Cu^{2+}, and Zn^{2+} in superoxide dismutase (*2*), Zn^{2+} in carboxypeptidase, and carbonic anhydrase (*3*, *4*)

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and Ni^{2+} in urease (*5*). On the other hand, metal ions such as Cd^{2+}, Hg^{2+}, and Pb^{2+} are well documented in the literature to be harmful to our ecosystem (*6–10*). In this context, the itai–itai (*9*) and minamata (*10*) diseases caused by Cd^{2+} and Hg^{2+}, respectively, are well documented in the literature. Hence, accurate qualitative and quantitative sensing of ions has topped the agendas of chemists for the last couple of decades. In this regard, colorimetric sensors are especially attractive because they would allow 'naked-eye' detection of ions without resort to any costly spectroscopic instrumentation.

This study is part of our current research interest directed toward synthesis, characterization, and evaluation of colorimetric receptors for ions of biological and environmental relevance (*11–15*). The selection of sulfa drugs as the starting material for this study was based on their ready availability, low price, and the presence of ligating groups. Sulfonamide and its substituted derivatives are extensively used in medicine for their antibacterial properties (*16–19*). In the field of ion sensing, very few sulfa drug derivatives have been used as a constituent of molecular chemosensors for cations. In contrast, several sulfa drug-based receptors have been reported in the literature for anions (*20–23*).

We report herein the synthesis and characterization of two diazo derivatives of sulfathiazole (**R1**) and sulfamethoxazole (**R2**). Both the compounds (**R1** and **R2**) were further screened for their possible use in metal ion recognition. Compound **R1** showed solvatochromism and solvent-assisted naked-eye sensing for Hg^{2+}, while **R2**, which is an oxygen analog of **R1**, was unable to show any sensing behavior toward Hg^{2+}.

2. Results and discussion

2.1. *Crystal structure of compounds R1 and R2*

The relevant crystal structure data along with structure determination details of compounds **R1** and **R2** are given in Table 1.

A perusal of Table 1 clearly showed that both **R1** and **R2** adopted a triclinic pattern with $P-1$ symmetry. The N3−N4 bond lengths in **R1** and **R2** were found to be 1.30 and 1.31 Å, respectively, which matched well with N−N bond lengths reported in the literature (*11*). Thus, it was concluded that both **R1** and **R2** existed in their hydrazo rather than azo forms (Figure 1).

2.2. *Sensing studies*

2.2.1. *UV–visible studies*

The UV–visible spectra of **R1** and **R2** showed broad absorption bands in nujol at 409, and 358 nm and at 390 and 353 nm, respectively. **R1** was absorbed at 493 and 411 nm at 1×10^{-3} M in DMSO solution, while **R2** did not show any variation in λ_{max} in DMSO in comparison to nujol. Hence, only **R1** was studied in a series of solvents having different polarities with the results summarized in Table 2. The corresponding UV–visible absorption spectra and color changes are given in Figure 2.

As it can be seen from Table 2 and Figure 2, **R1** showed an additional broad peak at 480–493 nm in polar solvents such as DMSO, DMF, and acetone, due to the formation of an intermolecular hydrogen bond as shown in Scheme 1.

The solvent-sensitive peak at 493 nm is responsible for the orange color of **R1** in these solvents, while in other solvents, without an X=O group (where X=S, C, or N), neither this broad solvent-assisted peak nor the orange red color was observed. The non-occurrence of solvatochromic

Table 1. Crystal data and structure refinements for compounds **R1** and **R2**.

Identification code	Compound **R1**	Compound **R2**
CCDC number	706686	746351
Empirical formula	$C_{17}H_{21}N_4O_5S_2$	$C_{15}H_{16}N_4O_5S$
Formula weight	425.50	364.38
Crystal system	Triclinic	Triclinic
Space group	$P-1$	$P-1$
T (K)	100 (2)	100 (2)
λ, MoKα	0.71069	0.71069
a (Å)	7.977(5)	5.455(5)
b (Å)	8.980(5)	10.835(5)
c (Å)	14.569(5)	14.479(5)
α (°)	87.238(5)	93.850(5)
β (°)	74.525(5)	100.553(5)
γ (°)	78.945(5)	90.814(5)
V (Å^3)	987.1(9)	839.1(9)
Z, ρ_{calc} (Mg m^{-3})	2, 1.432	2, 1.442
μ (mm^{-1})	0.307	0.228
F (0 0 0)	444	380
Crystal size (mm^3)	0.20 × 0.16 × 0.14	0.15 × 0.09 × 0.05
θ range for data collection	2.3–27.9	2.3–28.8
Index ranges	$-10 <= h <= 10$, $-11 <= k <= 8$, $-18 <= l <= 19$	$-7 <= h <= 7$, $-11 <= k <= 14$, $-18 <= l <= 19$
Reflections collected	6475	6834
Reflections/restraints/parameters	4660/0/253	3753/0/234
Goodness-of-fit on F^2	1.101	1.104
$R1$[a], $wR2$[b] ($I > 2\sigma(I)$)	0.0715/0.2006	0.0407/0.1226
$R1$[a], $wR2$[b] (all data)	0.0991/0.2610	0.0480/0.1256
Largest difference peak/hole, e Å^{-3}	0.623/−0.467	0.401/−0.327

Notes: [a]$R = \Sigma\|F_o| - |F_c\|/\Sigma|F_o|$.
[b]$wR2 = \{\Sigma[w[(F_o^2 - Fc^2)^2]/\Sigma[w(Fo^2)^2]\}^{1/2}$.

behavior in **R2** may be a consequence of the presence of the oxygen-containing oxazole ring in place of the sulfur-containing thiazole ring in **R1**. This observation is a consequence of a substituent effect, which is in accordance with a literature report (*24*).

Due to the presence of the solvent-assisted peak and orange color of compound **R1**, we further screened this compound for its possible use in the field of metal ion sensing. The 1.0×10^{-3} M DMSO solution of compound **R1** was treated with one equivalent of d^{10} metal ions as their chloride salts. Among the d^{10} metal ions, only Hg^{2+} showed a naked-eye color change from orange to olive green with the 493 nm band nearly vanishing for compound **R1** (Figure 3 and Table 3) for this ion. The rest of the d^{10} metal ions (Zn^{2+} and Cd^{2+}) were not able to produce any significant spectral or naked-eye color changes.

In order to further understand the binding characteristics of **R1** toward Hg^{2+}, UV–visible titration studies were also performed. On concomitant additions of Hg^{2+} (as its chloride salt) to the 1.0×10^{-3} M DMSO solution of **R1**, the solvent-assisted band at 493 nm started vanishing, and it was almost vanished on the addition of two equivalents of Hg^{2+}. At this stage, the color of the **R1** solution turned olive green from orange, which is easily observable to the naked-eye. Further addition of Hg^{2+} up to 3.0 equivalents did not produce any UV–visible spectral or naked-eye color change (Figure 4).

The non-linear fitting of UV–visible titration data for compound **R1** was done with the 1:2 ([G]/[H]) binding equation (*25*), yielding an association constant of $(1.48 \pm 0.05) \times 10^3$ M^{-2} with a satisfactory correlation coefficient value $r^2 = 0.9985$ (Figure 5). The 1:2 binding stoichiometry between Hg^{2+} and **R1** was also confirmed by mass spectrometric studies for **R1**+$HgCl_2$ that yielded an (M+H) peak at 932.4 (see ESI; Figure S5) as expected for its mass.

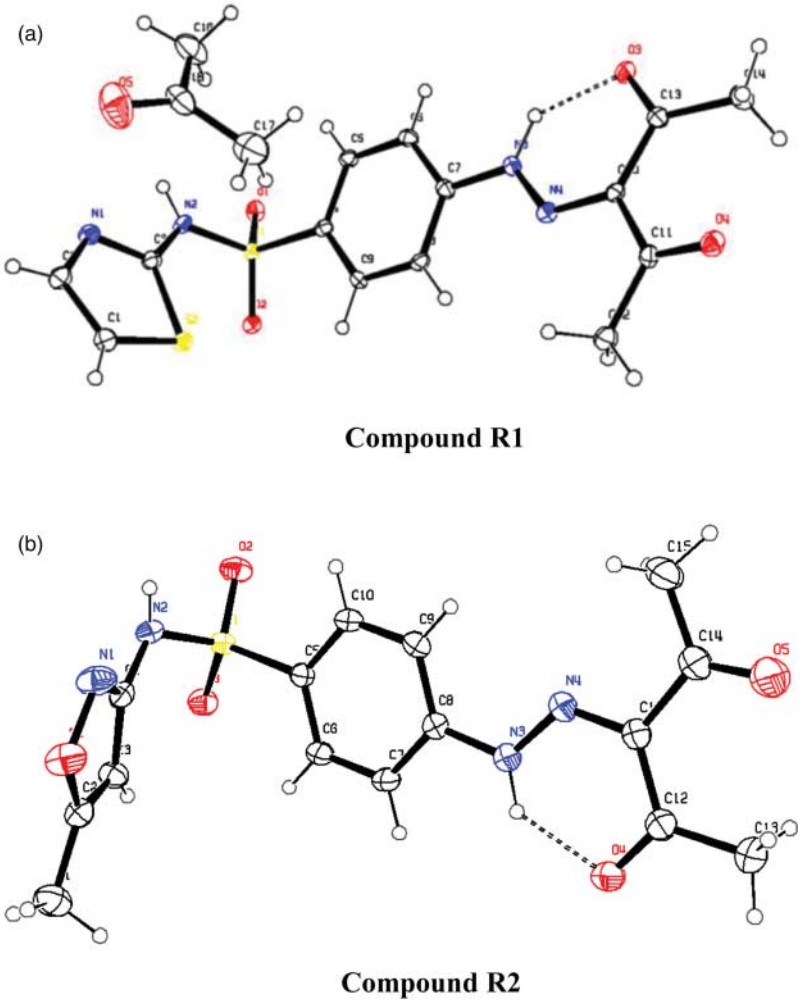


Figure 1. X-ray crystal structure of compounds **R1** and **R2** (ORTEP diagram).

Table 2. UV–visible absorption bands of **R1** in solid and solution states.

S.no.	Medium	UV–visible bands (nm)
1	Nujol	409, 358
2	DMSO	493, 411
3	DMF	480, 409
4	Acetonitrile	404, 306
5	Acetone	490, 404, 354
6	Chloroform	409

Similar additions of Zn^{2+} and Cd^{2+} as their chloride salts to 1.0×10^{-3} M DMSO solutions of **R1** did not produce any significant visible spectral changes (Figure 3). The change of the counter anion of Hg^{2+} did not affect its interaction with **R1** either in terms of naked-eye or spectral changes. Hg^{2+} sensitive papers (prepared by soaking the strips of Wattman filter paper No. 42 in a saturated solution of the **R1** in DMSO) produced similar types of naked-eye changes when they

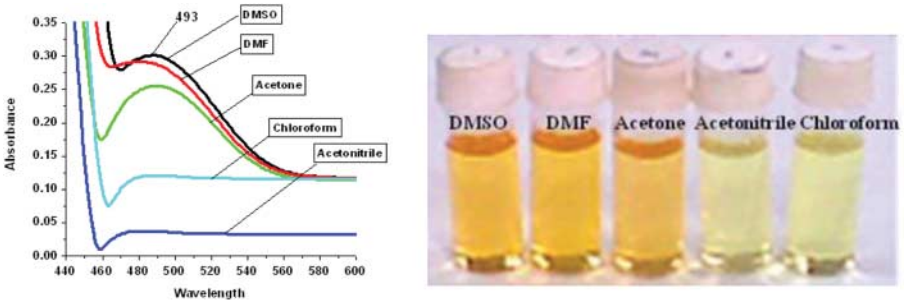
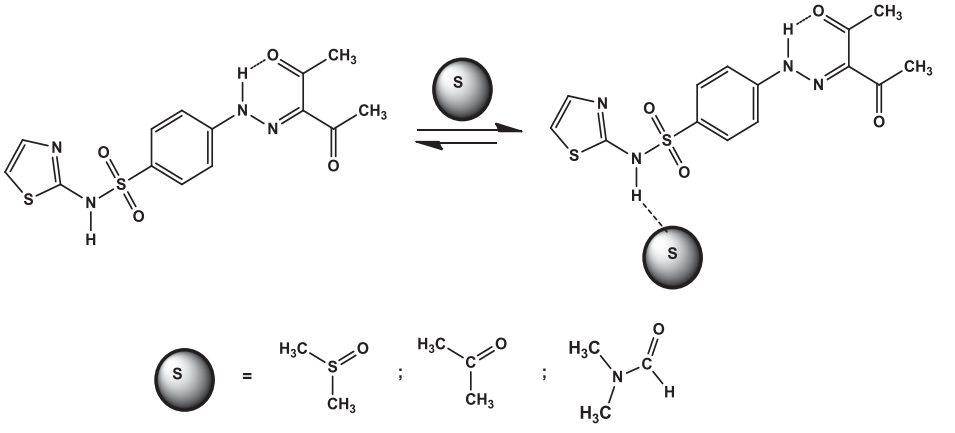


Figure 2. Absorption spectra of 1×10^{-3} M DMSO solution of **R1** in different solvents and respective color changes.



Scheme 1. Weak interaction of polar solvents with compound **R1**.

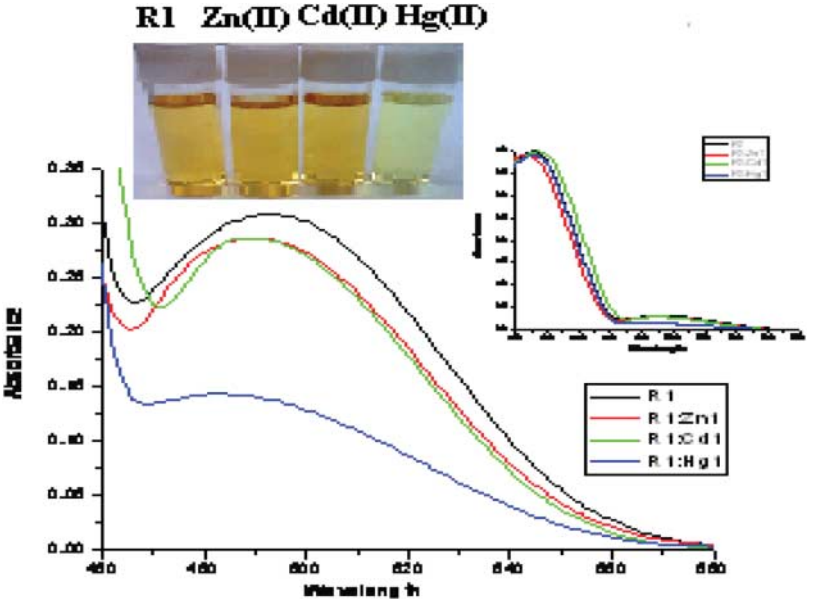


Figure 3. Absorption spectral pattern of 1×10^{-3} M DMSO solution of **R1** on addition of 1.0 equivalents of Zn^{2+}, Cd^{2+}, and Hg^{2+}.

Table 3. UV–visible spectral bands and color changes of 1.0×10^{-3} M DMSO solution of **R1** on separate addition of 1.0 equivalents each of Zn^{2+}, Cd^{2+}, and Hg^{2+} as their chloride salts.

Species	Color	Wavelength (nm)
R1	Orange	493, 411
R1:Zn^{2+}	Dark orange	491, 406
R1:Cd^{2+}	Dark orange	490, 416
R1:Hg^{2+}	Olive green	493, 412

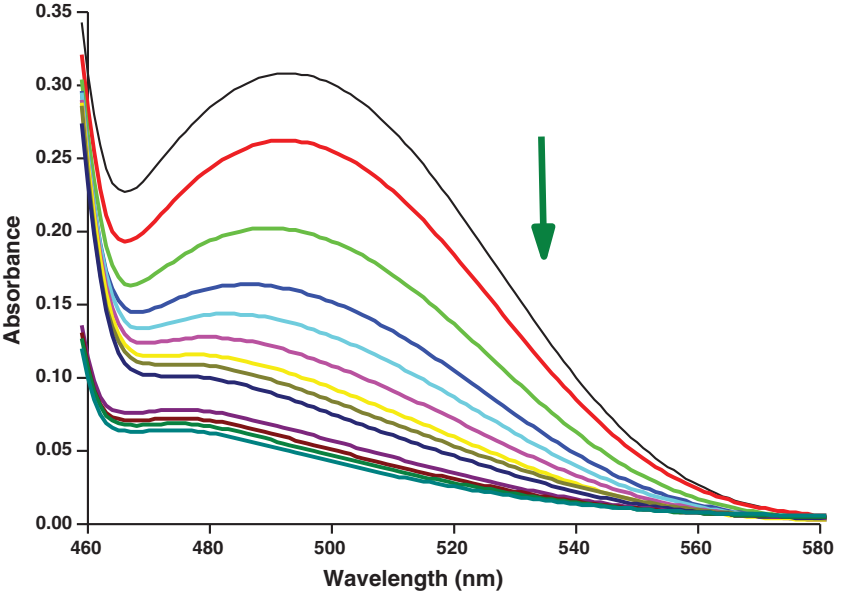


Figure 4. Absorption spectra of 1×10^{-3} M DMSO solution of **R1** on concomitant addition of 0.0–3.0 equivalents of Hg^{2+}.

were dipped into solutions of Hg^{2+} in DMSO, while they did not produce any color change by dipping into the respective solutions of Zn^{2+} and Cd^{2+} (Figure 6).

2.2.2. ^1H *NMR titration studies*

To further look into the nature of host–guest interactions, ^{1}H NMR titration experiments (see ESI; ESI; Figure S6 and S7) were performed by adding varying equivalents of Hg^{2+} (0–3 equivalents) as its chloride salt to a 5×10^{-3} M DMSO-d_6 solution of **R1**. The chemical shifts in δ ppm for –NH protons are given in Table 4. When comparing the two NHs of compound **R1**, the proton at N-3 absorbed downfield (13.63 δ ppm) in comparison to N-2 (12.71 δ ppm). The downfield shifting of the NH at N-3 position in DMSO-d_6 may be a consequence of intramolecular hydrogen bonding with $COCH_3$ (one of acetyl group of **R1**), which was further supported by the dilution experiment with $CDCl_3$ (see ESI; Figure S8).

The most important change upon concomitant additions of Hg^{2+} to **R1** was the gradual vanishing of the N-2H proton signal. The complete vanishing of this proton was achieved upon the addition of 2.0 equivalents of Hg^{2+}, indicating the loss of N-2H as the result of its complexation with $HgCl_2$.

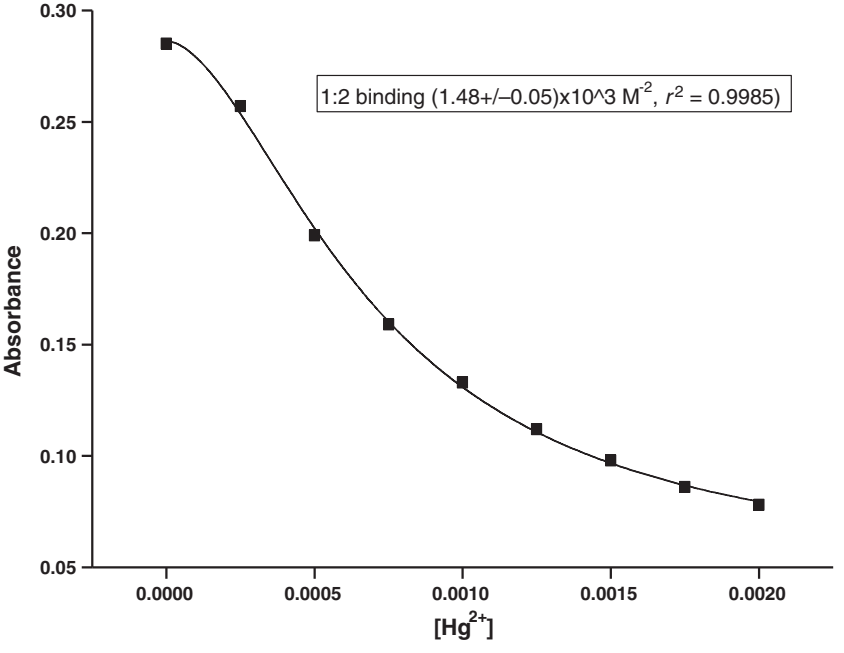


Figure 5. Binding curve for 1:2 binding between **R1** and Hg^{2+} as its chloride salt in DMSO.

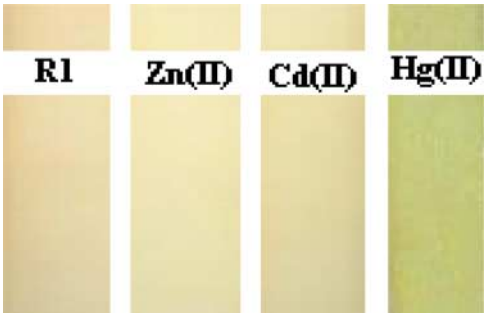
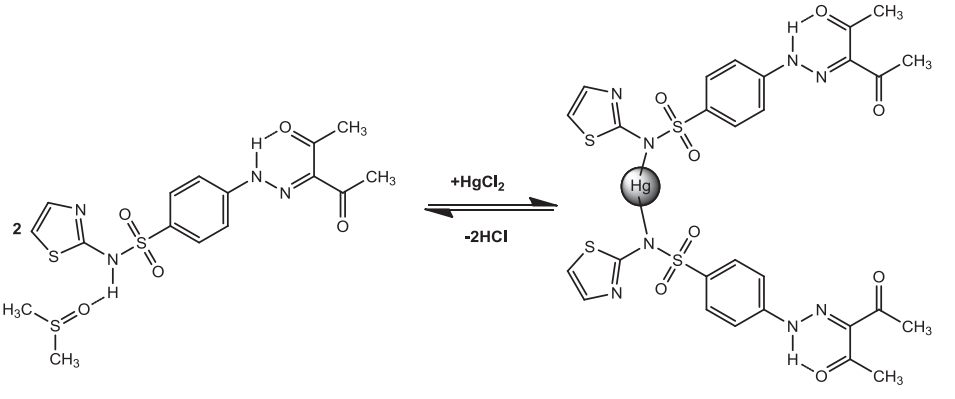


Figure 6. Compound **R1** strips showing color changes on dipping into the DMSO solution of d^{10} metal ions.

Table 4. ^1H NMR spectral titration data of 1×10^{-3} M DMSO-d_6 solution of **R1** on the concomitant addition of Hg^{2+} (0–3 equivalents) as its chloride salt (12.4–13.9 δ ppm).

Equivalents of Hg^{2+}	Chemical shifts in (δ ppm)	
	N–H(N-3)	N–H(N-2)
0.00	13.63	12.71
0.25	13.64	12.73
0.50	13.64	12.73
0.75	13.64	12.75
1.00	13.64	12.71
1.25	13.64	12.73
1.50	13.65	12.71
1.75	13.65	12.66
2.00	13.65	–
2.50	13.65	–
3.00	13.66	–

Thus, on the basis of UV–visible and ^{1}H NMR titrations, additional support from mass spectral data, (**R1**+$HgCl_2$) that forms in DMSO in an equilibrium process (Scheme 2), may be proposed as being responsible for the naked-eye sensing of Hg^{2+} by **R1**. However, in this study, the sensing pathway involves a 1:2 ([G]/[H]) stoichiometry, compared to 1:1 in our previous report (*12*).



Scheme 2. Chemical structure image of binding of compound **R1** with Hg^{2+}.

3. Experimental

3.1. *Apparatus*

The IR Spectra were recorded as KBr pellets on a Varian 3100 FT–IR spectrophotometer, while UV–visible spectral studies were performed on a UV-1700 pharmaspec UV–VIS spectrophotometer. The NMR spectral studies were performed on a JEOL AL 300 FT NMR spectrometer and the chemical shifts are reported in δ ppm using tetramethylsilane as the internal standard.

3.2. *Reagents and chemicals*

The sulfathiazole and sulfamethoxazole were purchased from Sigma (USA) and used without further purification, while sodium nitrite and sodium acetate were purchased from Qualigens Fine Chemicals, Mumbai. Acetyl acetone and diethyl ether were purchased from Spectrochem Pvt. Ltd., Mumbai. The remaining chemicals and solvents including spectroscopic grade DMSO were purchased from Central Drug House (P) Ltd., Delhi.

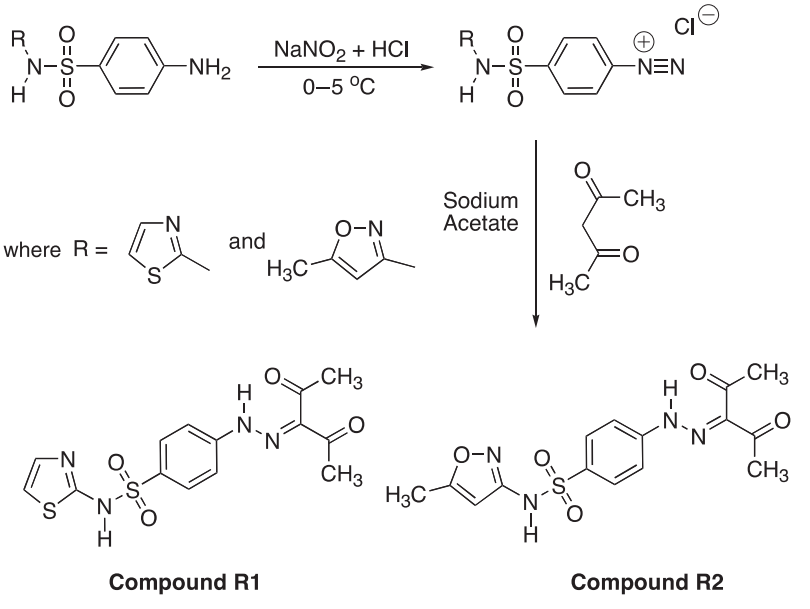
3.3. *X-ray diffraction studies*

Crystals of **R1** and **R2** of suitable sizes were grown by the slow evaporation of their supersaturated solutions in acetone and diethyl ether, respectively. The X-ray diffraction data for **R1** and **R2** were collected at 100 K on a Bruker SMART APEX CCD diffractometer using graphite-monochromated MoKα radiation ($\lambda = 0.71069$ Å). The linear absorption coefficients, scattering factors for the atoms, and the anomalous dispersion corrections were taken from international tables for X-ray crystallography. The data integration and reduction were processed with SAINT (*26*) software. An empirical absorption correction was applied to the collected reflections with SADABS (*27*) using XPREP (*28*). The crystal structures were solved by the direct method using SHELXTL (*29*) and refinements were done on F^2 by a full-matrix least-squares technique using

the SHELXL-97 (*30*) program package. For all the cases, non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were fixed geometrically and treated as riding atoms using SHELXL default parameters.

3.4. *Synthesis of compounds R1 and R2*

Compounds **R1** and **R2** (Scheme 3) were synthesized according to a general literature procedure (*31–33*). These were fully characterized by single crystal X-ray diffraction studies in conjunction with IR, ^{1}H NMR, and mass spectral studies (see ESI; Figure S1–S4).



Scheme 3. Synthetic procedure for compounds **R1** and **R2.**

Conclusion

Thus, two diazo derivatives of sulfa drugs (**R1** and **R2**) derived from the diazotization of sulfathiazole and sulfamethoxazole and their subsequent couplings over 2,4-pentanediaone are being reported. These compounds were fully characterized by single crystal X-ray diffraction studies. We were successful in establishing the use of **R1** for the naked-eye recognition of a notorious toxic metal ion like Hg^{2+} at a milimolar level.

Acknowledgements

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Supplementary material

Crystallographic data for the structures reported in this article have been deposited with the Cambridge Crystallographic Data Centre (The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; email: deposit@ccdc.cam.ac.uk; www: http://www.ccdc.cam.ac.uk; fax: 44 1223 336033) and are available free of charge on request, quoting the Deposition No. CCDC 706686 for compound **R1** and 746351 for compound **R2**.

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