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### Efficient eco-friendly syntheses of dithiocarbazates and thiosemicarbazones

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## Efficient eco-friendly syntheses of dithiocarbazates and thiosemicarbazones

Nur Halilatul Sadiqin O. Ali<sup>a</sup>, Malai Haniti S. A. Hamid<sup>a</sup>, Nurul Amirah 'Aqilah Mohamad 'Asri Putra<sup>a</sup>, Hajar Azirah Adol<sup>a</sup>, Aminul Huq Mirza<sup>a</sup>, Anwar Usman<sup>a</sup>, Tasneem A. Siddiquee<sup>b</sup>, Md. Rejaul Hoq<sup>b</sup> and Mohammad R. Karim<sup>b</sup>

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### ABSTRACT

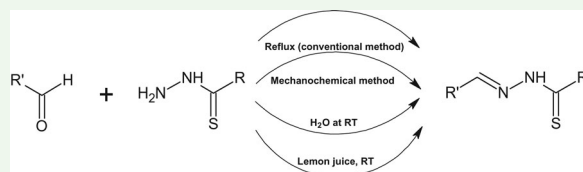
Eight Schiff bases have been synthesized by conventional and three different eco-friendly methods, whereby two aromatic carbonyl compounds *viz.* 2-thiophenecarboxaldehyde and salicylaldehyde were reacted with *S*-methyl, *S*-benzyl, and *S*-*n*-octyl-dithiocarbazates and thiosemicarbazide. In order to evaluate the efficiency of the synthesis methods, the time to complete the reaction and the yield of the Schiff base synthesized by eco-friendly methods, such as solvent-free grinding, water as a solvent, and lemon juice as catalyst, were compared with those synthesized by the conventional method. The chemical structures of all the synthesized Schiff bases, where two of them are novel and reported for the first time, were fully characterized by a variety of physico-chemical, analytical, and spectroscopic techniques. The molecular and crystal structures of the Schiff bases especially those having 2-thiophene moiety were further elucidated by single crystal X-ray diffraction analyzes.

### ARTICLE HISTORY

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Eco-friendly synthesis; Schiff bases; Thiosemicarbazones; Dithiocarbazates; Crystal structures






## Introduction

The concept of green synthesis and its applications in various organic syntheses by utilizing solvent-free processes is to avoid pollution (1, 2). Ideally, these so-called eco-friendly processes do not require the use of harmful solvents and produce minimum wastes, therefore minimizing pollution and having less environmental impact. Some criteria for the ideal synthesis include atom efficient, simple, 100% yield, easily available materials, environmentally acceptable, no wasted reagents, one step, and safe, as it has been described in detail by Clark (3). Environmentally compassionate synthesis methods therefore have received considerable attention and, recently, some solvent-free procedures for the synthesis of Schiff bases have also been developed (4, 5). As it has been elegantly described by Sheldon, *the best solvent is no solvent and if a solvent (diluent) is needed then water is preferred* (6). The synthesis of Schiff bases by solvent-free reaction using mechanical grinding or

mechanochemical reaction (7) was first reported by Fumio Toda *et al.* (8). By grinding together solid anilines with solid benzaldehydes without passing through liquid phases, Toda *et al.* reported the syntheses of twenty azomethines in 100% quantitative yield as hydrates. It was concluded that the solid–solid condensations were essentially “waste-free” unlike acid-catalyzed azomethine syntheses in solution and the ease of these reactions relied on the crystal packing. However, great interest has been focused on the use of ball milling techniques as described by Wang (9) and Tigineh *et al.* (4).

Schiff bases of *S*-alkyl/aryl dithiocarbazates and thiosemicarbazide containing the azomethine group (–CH=N–) have attracted much attention because of their diverse biological and pharmacological properties (10–12). In particular, heterocyclic thiosemicarbazones have antibacterial, antimalarial, antiviral, and antitumour activities. Thiosemicarbazones were the first true antiviral substances synthesized and their potential was only

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realized after a number of random events had taken place (13). In fact, thiosemicarbazones were the first compounds found to be antiviral active in virus-infected animal tests (13). Among all the thiosemicarbazones and dithiocarbazates studied so far, the compound that has attracted considerable attention as a potent anticancer agent is triapine (3-aminopyridine-2-carboxaldehydethiosemicarbazone). It is an experimental drug that has entered several Phase I and Phase II clinical trials as an anticancer chemotherapeutic agent (14). It also has intrinsic fluorescent properties at 360 nm which enable researchers to monitor the uptake and intracellular distribution of this drug in human cancer cells.

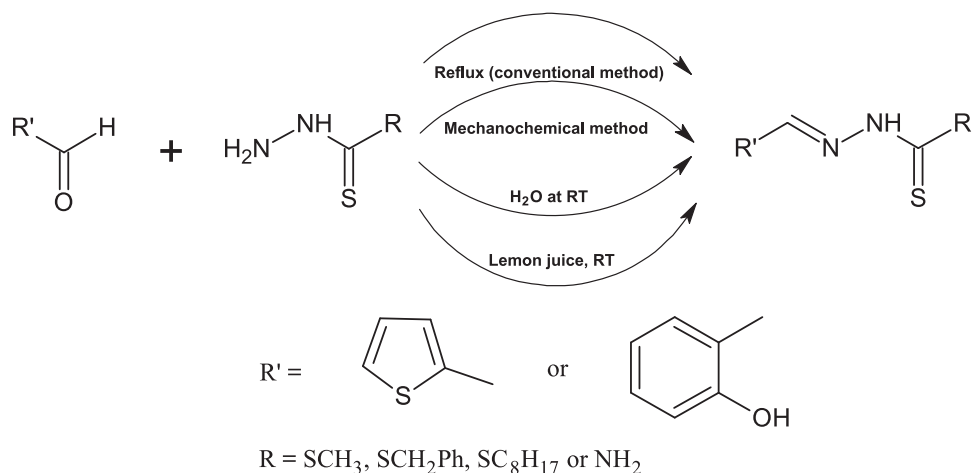
In view of potentially beneficial activities of dithiocarbazates and thiosemicarbazones, we hereby report eight Schiff bases (labeled as **1–8**, Scheme 1, Table 1) that have been successfully synthesized from the reactions of 2-thiophenecarboxaldehyde, a heterocyclic aldehyde (15) and salicylaldehyde, a commonly used aldehyde in the synthesis of Schiff bases (4, 16), with *S*-methyl, *S*-benzyl, *S*-*n*-octyldithiocarbazates and thiosemicarbazide by the conventional method and eco-friendly methods, namely (i) the solvent-free grinding or mechanochemical method, (ii) the use of water as solvent at room temperature and (iii) the use of lemon juice (*Citrus limonium*) as catalyst. We have been able to synthesize the Schiff bases in moderate to excellent yields. To the best of our knowledge, this is the first paper that describes the green syntheses of the Schiff bases obtained from these types of amino compounds. We then compared the yield of respective Schiff bases obtained from each method with those obtained from their conventional method. The relatively high yields were obtained by the eco-friendly methods, and syntheses were much easier and faster than the conventional method. This

reflects the high atom economy obtained and the eco-friendly nature of the methods described.

## Results and discussion

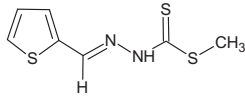
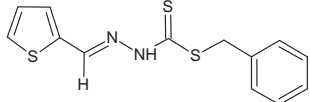
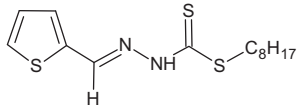
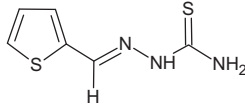
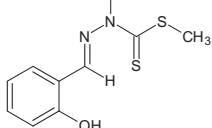
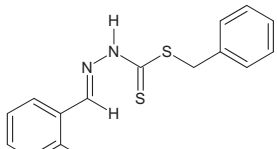
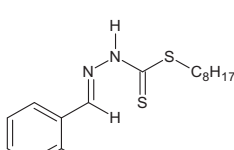
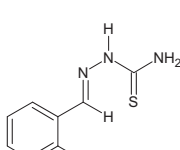
To date, there are no studies on the green syntheses of thiosemicarbazones and dithiocarbazates, although Sachdeva *et al.* have reported on the syntheses of some new Schiff bases from the reaction of amino acids with thiosemicarbazide and the compounds were found to be active against tested pathogens (17). The solvent-free mechanochemical synthesis (4, 5, 18), water as solvent (19), and the use of lemon juice (17, 20) as catalyst have been utilized in the syntheses of Schiff bases, but these methods are mainly using primary aromatic amines as the amino compound. The fact that these methods which use inexpensive and straightforward preparations lead us to explore their potential in the synthesis of thiosemicarbazones and dithiocarbazates in our laboratory. The recrystallized yield and time taken for complete conversion of eight Schiff bases that we have synthesized using the eco-friendly methods are summarized in Table 1 along with those synthesized by the conventional method. For the conventional and three green methods, the progress of the reaction was monitored by TLC every 10–15 min and the time needed for completion of reaction was recorded. Details of the synthesis procedures and chemical characterizations of the products are included in the experimental section. As shown in Table 1, the amines used in the reactions are *S*-alkyl/aryl dithiocarbazates and thiosemicarbazides.

Taking Schiff base **1**, as an example, the conventional method involved heating at reflux using a suitable solvent (typically absolute EtOH) until the reaction has completed, and progress of the reaction was monitored



**Scheme 1.** Synthesis of dithiocarbazates and thiosemicarbazones.

**Table 1.** The yields obtained and times taken for complete conversion of Schiff-bases (1–8) using conventional and eco-friendly methods.

No	Schiff Base	Conventional Method		Mechanochemical Method <sup>a</sup>		Water as Solvent <sup>a</sup>		Lemon juice as Catalyst <sup>a</sup>	
		Time (min)	Yield (%) <sup>b</sup>	Time (min)	Yield (%) <sup>b</sup>	Time (min)	Yield (%) <sup>b</sup>	Time (min)	Yield (%) <sup>b</sup>
1		180	74	25	91	120	92	20	79
2		300	57	20	72	30	95	60	89
3		120	46	15	83	30	95	60	93
4		180	83	20	80	35	96	60	82
5		45	79	30	77	30	62	30	78
6		60	83	20	86	30	72%	60	79
7		240	36	15	92	30	90	60	91
8		150	59	20	79	90	62	45	60

<sup>a</sup>Eco-friendly or green methods.<sup>b</sup>Recrystallized yield.

by TLC and the crude product obtained was recrystallized to give 74% yield. Heating by conventional method has been known to be time consuming and produce toxic wastes (21). As shown in Table 1, the time of reflux is 180 min. For the mechanochemical or grinding method, both the aldehyde and the amino compound are placed in a mortar and were ground. A paste is typically obtained while grinding, indicating that the reaction has taken place. The time needed for complete conversion was much less (25 min) and the recrystallized yield obtained was 91%. For the reaction

using water as solvent, however, both the aldehyde and the amino compound were added to water (typically 10 mL) and left to stir at room temperature. The time needed for complete conversion was 120 min and the recrystallized yield obtained was 92%. As for the reaction using lemon juice as catalyst, both the aldehyde and the amino compound were added into a small conical flask and lemon juice (0.5–1 mL) was added with stirring at room temperature. The time needed for complete conversion was the shortest (20 min) and the recrystallized yield obtained was 79%.

For the mechanochemical methodology, where the synthesis was carried out under solvent-free conditions at room temperature, the Schiff bases were obtained at shorter reaction time (15–30 min) and generally higher yields (72–92%) as compared to the conventional method (36–83%), as shown in Table 1. Similarly to a typical mechanochemical synthesis, a fast color change was observed and was related to a dehydration process (4). The yields listed out in Table 1 are the recrystallized yields obtained after recrystallization of the crude product that was obtained quantitatively after grinding.

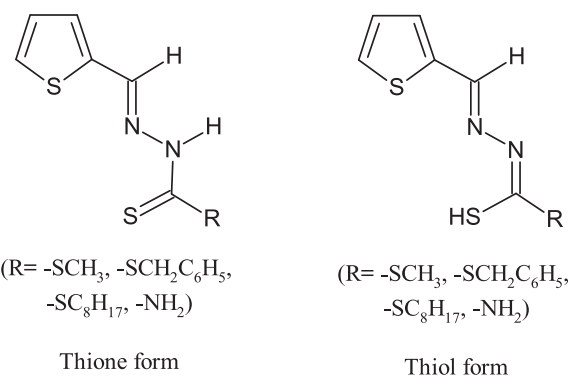
For the use of water as solvent in the synthesis, it was convenient that the Schiff base products were insoluble in water and the work-up of the reaction simply requires gravity filtration to isolate the product. After the crude product was obtained quantitatively, it was then recrystallized from absolute EtOH to give moderate to excellent yields (62–96%). There are at least three factors attributing to the feasibility of the synthesis in water (16), namely, hydrophobic effect, enhanced hydrogen bonding in the transition state (22–24), and the high cohesive energy density of water (25, 26). These factors have been described in great detail by Rao *et al* (19). It is also worth noting that, our observation during the synthesis, since both aldehydes are liquids, a small scale synthesis (0.5 mmol of starting materials) tends to give a full conversion to the product at a much shorter time (10–15 mins).

For the methodology that uses lemon juice (*Citrus limonium*) as catalyst, the Schiff bases were generally obtained at shorter reaction time (20–60 min) and generally higher yields (60–93%) as compared to the conventional method. Lemon juice is of the choice for catalyst because it is environmentally benign and is a green alternative to acid catalysts used in synthesis (27). The lemon juice obtained was filtered through a filter paper and the pH was recorded (pH = 2.3–2.5). The reaction was done at room temperature with stirring. A small amount of EtOH was added to ensure smooth stirring. Work-up was simply done by gravity filtration of the crude mixture, washing with cold EtOH, and followed by recrystallization from a suitable solvent. The Schiff bases synthesized by this method were obtained from moderate to excellent yields.

Overall, the yields obtained by the green methods are better or comparable with the yields obtained by conventional method except for Schiff base 5 (see Table 1).

### <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) Spectra

Compounds containing the thioamide –N–NH–C(=S) moiety like other thiosemicarbazones and the Schiff bases derived from *S*-alkyl/aryldithiocarbazates are capable of exhibiting thione-thiol tautomerism or as an



**Figure 1.** The thione and thiol forms of **1–4**.

equilibrium mixture of both forms. Taking 2-thiophene-carboxaldehyde Schiff base as an example (Figure 1), the thione-thiol tautomeric forms are shown for the four Schiff bases (labeled as **1–4**).

In general, the <sup>1</sup>H NMR spectra of all the Schiff bases show a singlet peak between δ 8.25–8.55 attributed to the azomethine (–CH=N) proton, peaks at δ 6.82–7.93 ppm attributed to aromatic protons and the least deshielded singlet peak of –SCH<sub>2</sub> or –SCH<sub>3</sub> is observed at δ 2.51–4.50 ppm. These results are similar to literature values (15, 28). Typically, these compounds in DMSO-d<sub>6</sub> could either adopt the *E* configuration with the –NH signal in the range of 9–12 ppm or adopt a *Z* configuration with the –NH signal in the range of 13–15 ppm (29, 30). Therefore, all the Schiff bases, except the thiosemicarbazones (**4** and **8**), exist as the *Z* isomer in DMSO-d<sub>6</sub> as evidenced by their –NH signals which are found between 13.21–13.38 ppm (31).

The <sup>1</sup>H NMR spectra do not show the –SH peak which is expected at δ 4.00 ppm, but instead, they show a singlet peak at δ 11.50–13.38 which is attributed to the secondary N–H atoms and this indicates that the Schiff bases in solution exist predominantly in thione form (32). Lastly, for the Schiff bases with the salicyl moiety, the –OH proton signal is observed at δ 9.95–10.50 ppm as expected (19, 33). For the two thiosemicarbazones, **4** and **8**, the two broad peaks appeared at δ 7.55 and 8.22 ppm, and 7.95 and 8.16, respectively, are attributed to the –NH<sub>2</sub> protons (34).

### <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) Spectra

The <sup>13</sup>C NMR spectra of all the Schiff bases show the signals assigned to the thione carbon (C=S) at 198.05–177.97 ppm, imine carbons (C=N) at 145.02–139.07 ppm, the signals assigned to the aromatic carbons at 116.47–138.39 ppm and the least deshielded signal assigned to the carbon of –SCH<sub>2</sub> or –SCH<sub>3</sub> at 17.20–38.01 ppm (28). Lastly, for the Schiff bases with the salicyl moiety, the signals at 157.70–156.85 ppm

are attributable to the hydroxyl carbon (C–OH) which is in agreement with literature values (35).

### Mass Spectra

The EI mass spectra shows molecular ion peaks at  $m/z$   $[M]^+$  that corresponds well to the proposed structures of all the Schiff bases (36). However, the molecular ion peaks for **2** and **3** are not found which is possibly due to all the molecular ions breaking into fragments.

### FTIR

In general, the IR spectra of all the Schiff bases display a strong band observed at around  $1578\text{--}1618\text{ cm}^{-1}$  which is assigned to the azomethine  $\nu(\text{C}=\text{N})$ . It is evident from the IR data that all the synthesized Schiff bases from *S*-alkyl/aryldithiocarbazate and thiosemicarbazide in the solid state display the secondary  $\nu(\text{N-H})$  band at  $3094\text{--}3132\text{ cm}^{-1}$  but do not show  $\nu(\text{S-H})$  band at  $2600\text{ cm}^{-1}$  indicating that in the solid state they remain as the thione tautomer (32). In addition, the thiosemicarbazones display stretching vibrations at  $3171\text{--}3231$  and  $3310\text{--}3410\text{ cm}^{-1}$  which are assigned as the asymmetric  $\nu(\text{N-H})$  and symmetric  $\nu(\text{N-H})$  of the  $\text{NH}_2$  group, respectively (29).

### X-ray Crystal studies

Besides carrying out a number of physico-chemical techniques including FTIR, NMR, and mass spectroscopy, as

previously described, we were able to grow single crystals for **1**, **3** and **4**. These compounds could therefore be conclusively be characterized. A summary of crystallographic data for Schiff bases **1**, **3** and **4** are summarized in Table 2.

Figures 2–4 show the molecular structures of **1**, **3** and **4**, respectively, with the atomic numbering and their intermolecular interactions in the crystal structure. Their 2-thiophenecarboxyl-thiocarbazate moiety are almost planar and the Schiff bases generally adopt the *E* conformation about the imine bond. Like most of thiosemicarbazones and Schiff bases from *S*-alkyl/aryl dithiocarbazates, the  $\text{C}=\text{S}$  and  $\text{C}=\text{N}$  bond lengths also indicate that, in the solid state, it remains in the thione form. Their bond lengths for azomethine are in the range of  $1.282(3)$  to  $1.290(3)\text{ \AA}$  that are similar to a typical  $\text{C}=\text{N}$  bond ( $1.268(4)$  to  $1.282(2)\text{ \AA}$ ) of related compounds (37, 38).

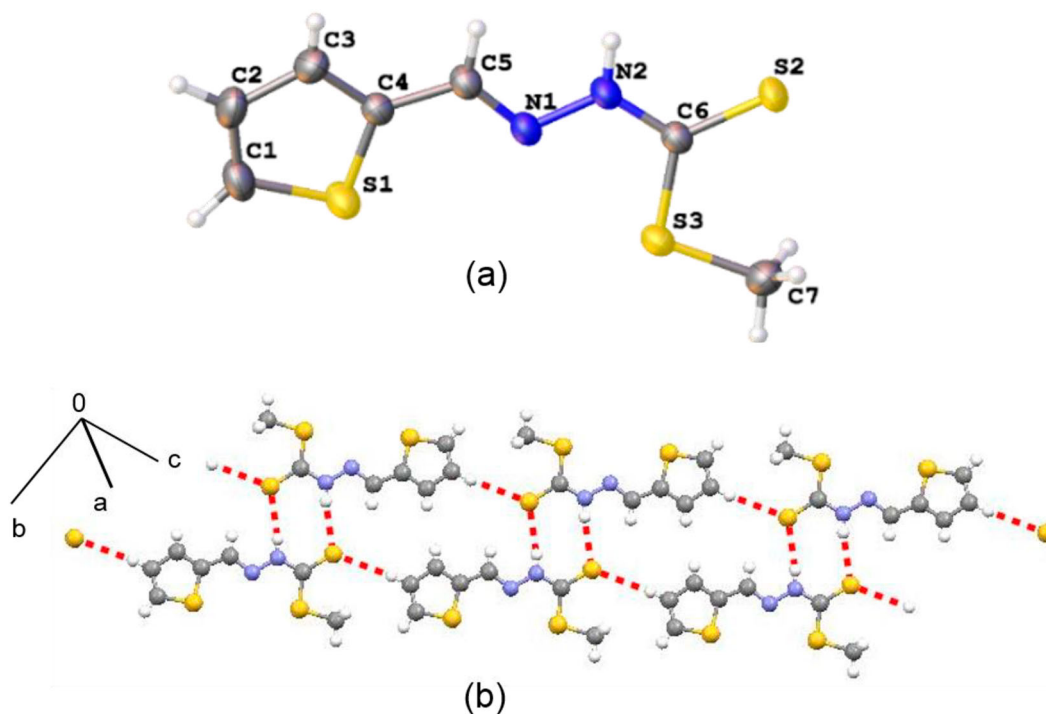
Schiff base **1** is nearly planar (Figure 2a) and molecules are interconnected by intermolecular  $\text{C-H}\dots\text{S}$  and  $\text{N-H}\dots\text{S}$  hydrogen bonds into molecular ribbons which are stacked on top of each other in the three dimensional structure (Figure 2b).

For Schiff base **3**, it undergoes conformational disorder in the crystal lattice, where the thiophene moiety is rotated by  $180^\circ$ , in such a way the molecules may adopt *E* and anti-*E* conformation with 50% probability (Figure 3a). Two molecules of **3** from adjacent asymmetric units are interconnected into head-to-head dimers by intermolecular  $\text{C-H}\dots\text{S}$  and  $\text{N-H}\dots\text{S}$  hydrogen bonds involving the thiocarbazate moiety. The dimers are further connected

**Table 2.** Crystallographic data and refinement data of Schiff bases 1, 3 and 4.

	1	3	4
Empirical formula	$\text{C}_7\text{H}_8\text{N}_2\text{S}_3$	$\text{C}_{14}\text{H}_{22}\text{N}_2\text{S}_3$	$\text{C}_6\text{H}_7\text{N}_3\text{S}_2$
Formula weight	216.33	314.51	185.27
Temperature/K	223(2)	100(2)	100(2)
Crystal system	triclinic	triclinic	monoclinic
Space group	<i>P</i> -1	<i>P</i> -1	$\text{P}2_1/\text{n}$
<i>a</i> /Å	6.068(5)	4.4599(2)	13.4386(6)
<i>b</i> /Å	9.058(7)	12.3610(4)	5.7674(3)
<i>c</i> /Å	9.762(7)	15.8193(6)	21.2745(9)
$\alpha^\circ$	68.70(2)	105.901(1)	90
$\beta^\circ$	81.48(3)	96.060(1)	96.280(1)
$\gamma^\circ$	79.72(3)	97.572(1)	90
Volume/Å <sup>3</sup>	489.8(7)	822.18(6)	1639.0(1)
<i>Z</i>	2	2	8
$\rho_{\text{calc}}/\text{cm}^{-3}$	1.4667	1.270	1.502
$\mu/\text{mm}^{-1}$	0.703	4.021	5.371
<i>F</i> (000)	224.8	336	768
Crystal size/mm <sup>3</sup>	$0.62 \times 0.56 \times 0.52$	$0.262 \times 0.240 \times 0.219$	$0.297 \times 0.285 \times 0.190$
$2\theta$ range for data collection/ $^\circ$	4.5–55.06	3.772–70.069	3.715–74.242
Index ranges	$-7 \leq h \leq 7$ , $-11 \leq k \leq 11$ , $-12 \leq l \leq 12$	$-5 \leq h \leq 5$ , $-15 \leq k \leq 15$ , $-19 \leq l \leq 19$	$-16 \leq h \leq 16$ , $-5 \leq k \leq 7$ , $-26 \leq l \leq 26$
Reflections collected	4832	17095	13345
Independent reflections	2107 [ $R_{\text{int}} = 0.0210$ ]	3123 [ $R_{\text{int}} = 0.0298$ ]	3232 [ $R_{\text{int}} = 0.0305$ ]
Data/restraints/parameters	2107/0/140	3123/185/223	3232/0/224
Goodness-of-fit on $F^2$	1.088	1.086	1.105
Final <i>R</i> indexes [ $I \geq 2\sigma(I)$ ]	$R_1 = 0.0289$ , $wR_2 = 0.0710$	$R_1 = 0.0265$ , $wR_2 = 0.0668$	$R_1 = 0.0357$ , $wR_2 = 0.1126$
Final <i>R</i> indexes [all data]	$R_1 = 0.0330$ , $wR_2 = 0.0740$	$R_1 = 0.0287$ , $wR_2 = 0.0717$	$R_1 = 0.0376$ , $wR_2 = 0.1143$
Largest diff. peak/hole/e Å <sup>-3</sup>	0.26/−0.24	0.258/−0.309	0.410/−0.487





**Figure 2.** (a) A view of the molecular structure of **1**, (b) molecules of **1** are interconnected by intermolecular C—H ... S and N—H ... S hydrogen bonds into molecular ribbons.

by other C—H ... S bonding interactions into molecular ribbons lying on the *bc*-plane. The dimers are stacked on top of each other along the *a*-axis (Figure 3b).

For Schiff base **4**, there are two molecules with the same conformation in the asymmetric unit similarly to the one reported by Hong *et al.* (15). The two molecules in an asymmetric unit are interconnected by an intermolecular N—H ... S hydrogen bond. They are further connected by intermolecular N—H ... S hydrogen bond into three dimensional structure (Figure 4).

## Conclusions

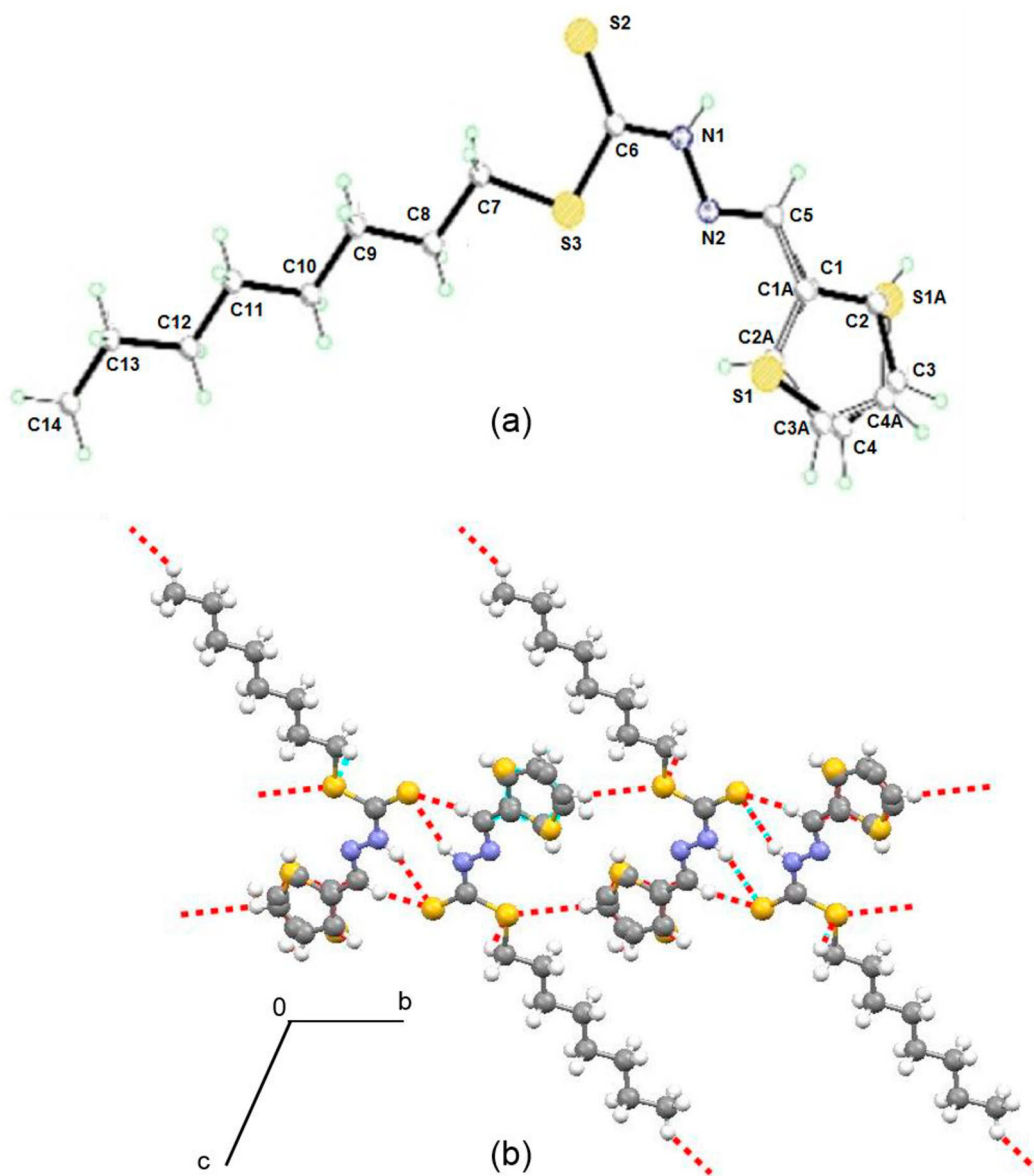
In summary, we have successfully synthesized eight Schiff bases from the reactions of 2-thiophenecarboxaldehyde and salicylaldehyde with *S*-methyl, *S*-benzyl and *S*-*n*-octyl-dithiocarbazates and thiosemicarbazide by both the conventional and three green synthesis methods including solvent-free grinding, water as solvent, and lemon juice as catalyst. The time required to complete the reaction and the yield of Schiff bases obtained by the different eco-friendly methods were compared with those of the conventional method. Our findings suggest that the water-based synthesis is most suitable for the Schiff base from thiophene-2-carboxaldehyde, whereas the grinding is best suited for the Schiff base from salicylaldehyde. Overall, the eco-friendly water-based and solvent-free grinding methods would

be a useful alternative green synthesis to the conventional method of any related Schiff bases in general.

## Experimental

### General

All the chemicals and solvents were of analytical reagent grade and used without any further purification. They were purchased from either Sigma-Aldrich, Merck or Fluka. The melting points of the compounds were determined by a melting point apparatus SMPi Stuart Scientific. TLC was performed using plastic plates with percoated silica, Whatman Partisil K6 60 TLC Plates fluorescent. The IR spectra were recorded using ATR in the frequency range of 4000–500  $\text{cm}^{-1}$  on a Shimadzu IR Prestige-21 Spectrometer. EI mass spectra were determined using an Agilent Mass spectrometer 5975C MSD (with direct probe). All of the experiments were carried out at the Faculty of Science, UBD. Melting point, IR and EI/MS were conducted at UBD.  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis and X-ray crystal diffraction were carried out at Tennessee State University, USA. Microanalyses for carbon, hydrogen and nitrogen (C, H, and N) were recorded on a Thermo Scientific CHNS Analyzer. Most of the X-ray data were collected using a Bruker AXS D8 VENTURE Single Crystal X-ray Diffractometer at the X-ray Diffraction Laboratory, Department of Chemistry, National University of Singapore



**Figure 3.** (a) A view of the molecular structure of **3**, (b) two molecules of **3** from adjacent asymmetric units are interconnected into head-to-head dimers by intermolecular C—H ... S and N—H ... S hydrogen bonds involving the thiocarbazate moiety. The dimers are further connected by other C—H ... S bonding interactions into molecular ribbons lying on the *bc*-plane.

(NUS). All IR and NMR spectra are included in the Supplementary Information.

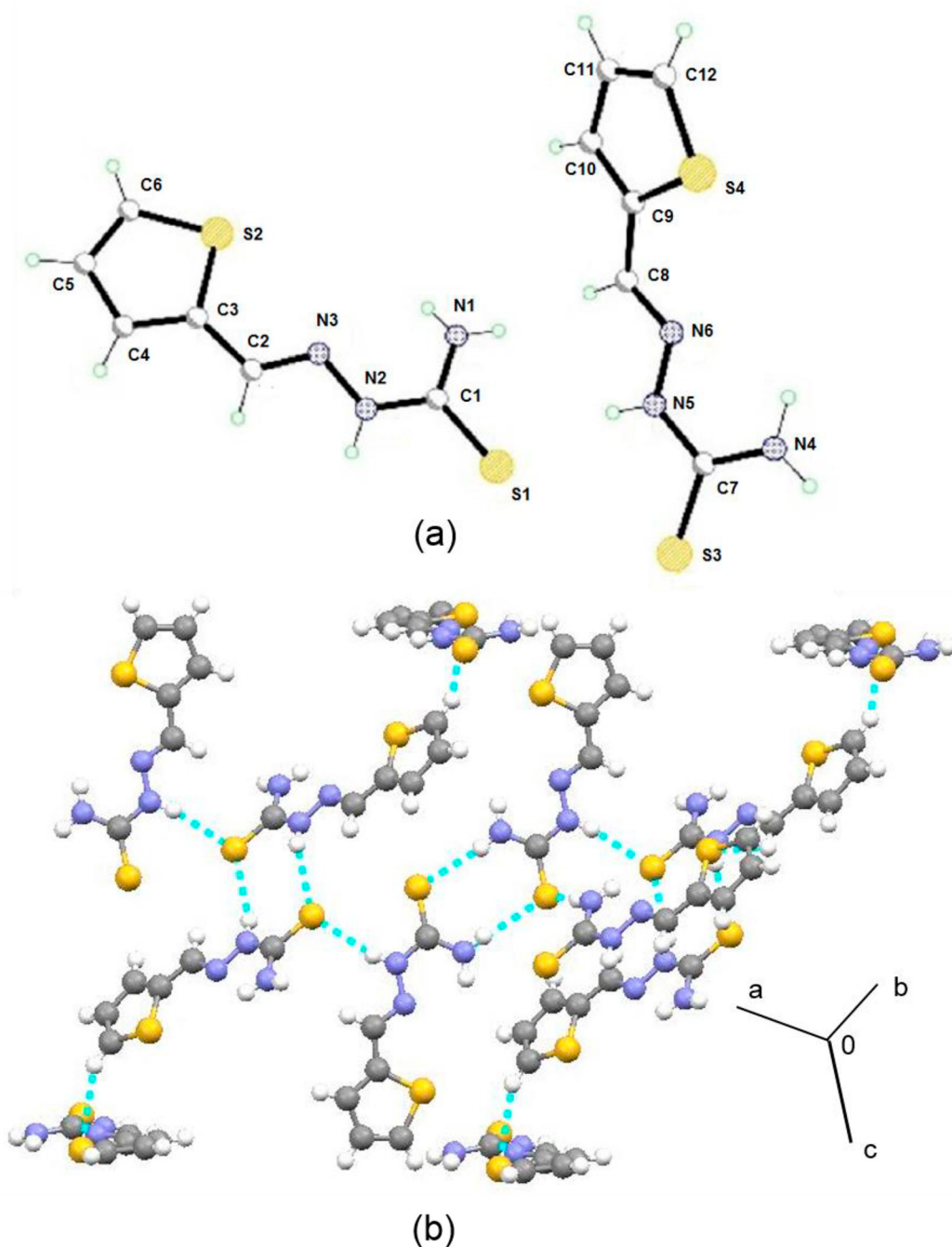
### General experimental procedures for Schiff Bases 1–8

#### Conventional method

In a typical reaction, a solution of the aldehyde (ranging from 4.5–9.0 mmol, 1 eq) in EtOH was added to an equimolar amount of amine in EtOH and heated under reflux for the respective time. The reaction mixture was left at room temperature overnight. The product obtained was filtered and washed with cold absolute EtOH and recrystallized from EtOH.

#### Solvent-free mechanochemical method

In a typical reaction, the aldehyde (ranging from 4.5–9.0 mmol, 1 eq) was added to an equimolar amount of the amino compound in a mortar and a color change was observed immediately. The mixture was then ground together at room temperature for the respective time needed (15–30 min). The progress of the reaction was monitored by TLC every 15–20 min. After completion, the powdered product was left in the mortar overnight, covered with watch glass and placed in a dark room. The product was collected by filtration, then washed with cold EtOH and recrystallized from absolute EtOH.



**Figure 4.** (a) A view of the molecular structure of **4** with two molecules with the same conformation in the asymmetric unit, (b) the two molecules of **4** in an asymmetric unit are interconnected by an intermolecular N—H ... S hydrogen bond to form a three dimensional structure.

#### *Water as solvent and stirring at room temperature*

For a small scale synthesis, 0.5 mmol of starting materials was used whilst 5 mmol scale of starting materials was used for a large scale synthesis. The amino compound that is not soluble in water was suspended in distilled water (10 mL) followed by the addition of the aldehyde to it at room temperature. However, if the amino compound is soluble in water, it is essential to add the

exact amount of water that is able to dissolve it completely. During the course of the reaction, some of the suspension turned yellow. The resulting mixture was then stirred at room temperature (ranging from 30 to 120 min) with monitoring by TLC every 15 min. The suspension turned pale yellow while still remaining undissolved from water and was left to stand overnight in a dark room to allow the solvent to dry out. The pale

yellow crude product obtained was collected by filtration, then washed with cold EtOH, and recrystallized from absolute EtOH.

### Lemon juice as catalyst (20, 39)

Firstly, fresh lemon fruit was cut and the pieces were squeezed manually to extract the juice. The juice obtained was then filtered through filter paper to remove the solid material and to get clearer juice which was used as a catalyst for the reaction. In a typical reaction, 1 mL lemon juice (pH 2.3–2.5) was added to a mixture of the amino compound (ranging from 4.5–9.0 mmol, 1 eq) and an equimolar amount of aldehyde. 1 mL absolute EtOH solvent was added to ensure smooth stirring. The mixture was stirred at room temperature (ranging from 20 to 60 min) with monitoring by TLC every 15 min. A color change is observed and the mixture was left to stand overnight in a dark room to allow the solvent to dry out. A pale yellow crude product was collected by filtration, then washed with cold EtOH and recrystallized from absolute EtOH.

Schiff bases **1–8** were prepared according to the above procedures and the analyses of Schiff bases **1, 2, 4, 5, 6** and **8** were consistent with literature values.

[Methyl (2*E*)-2-[(thiophen-2-yl)methylidene]hydrazine-1-carbodithioate] (**40**), (**1**). Yellow crystals; mp 184–186°C; Anal. Calc for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>S<sub>3</sub>: C 38.86, H, 3.73, N, 12.95%. Found: C 39.02, H 3.96, N 12.80%; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), δH: 13.29 (s, 1H, –NH), 8.40 (s, 1H, –CH=N), 7.69 (d, 1H), 7.15 (t, 1H), 7.51 (d, 1H) (thiophene-3H), 2.51 (s, 3H, –SCH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>), δC: 198.05 (–C=S), 141.97 (–CH=N), 138.22, 133.15, 130.52, 128.83 (heterocyclic carbons), 17.20 (–SCH<sub>3</sub>); IR (ν<sub>max</sub>, cm<sup>–1</sup>): 3098 ν(N–H), 1593 ν(C=N), 1028 ν(N–N), 927 ν(C=S); EI-MS Calc. for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>S<sub>3</sub> [M]<sup>+</sup>: 216.33, Found: 216.

[Benzyl (2*E*)-2-[(thiophen-2-yl)methylidene]hydrazine-1-carbodithioate] (**40**), (**2**). Yellow crystals; mp 188–190°C; Anal. Calc for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>S<sub>3</sub>: C 53.39, H 4.14, N 9.58%. Found: C 53.34, H 4.03, N 9.69%; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), δH: 13.35 (s, 1H, –NH), 8.40 (s, 1H, –CH=N), 7.68 (d, 1H), 7.14 (t, 1H), 7.51 (d, 1H) (thiophene-3H), 7.39 (d, 2H), 7.35 (t, 2H), 7.26 (t, 1H) (Ar-H), 4.46 (s, 2H, –SCH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>), δC: 196.10 (–C=S), 142.28 (–CH=N), 138.08, 137.25, 130.65, 127.77 (heterocyclic carbon), 133.33, 129.64, 129.01, 128.85 (aromatic carbon), 37.90 (–SCH<sub>2</sub>); IR (ν<sub>max</sub>, cm<sup>–1</sup>): 3103 ν(N–H), 1588 ν(C=N), 1031 ν(N–N), 923 ν(C=S).

[Octyl (2*E*)-2-[(thiophen-2-yl)methylidene]hydrazine-1-carbodithioate], (**3**). Pale yellow crystals; mp 82–84°C; Anal. Calc for C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>S<sub>3</sub>: C 53.46, H, 7.05, N, 8.91%. Found: C 53.32, H 6.88, N 8.62%; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>),

δH: 13.21 (s, 1H, –NH), 8.40 (s, 1H, –CH=N), 7.73 (d, 1H), 7.16 (t, 1H), 7.55 (d, 1H) (thiophene-3H), 3.17 (t, 2H, –SCH<sub>2</sub>), 1.65 (quint, 2H), 1.38 (m, 2H), 1.28 (m, 8H) (–CH<sub>2</sub>), 0.87 (t, 3H, –CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>), δC: 197.00 (–C=S), 141.90 (–CH=N), 138.39, 133.06, 130.51, 128.74 (heterocyclic carbons), 33.47 (–SCH<sub>2</sub>), 31.71, 29.05, 28.92, 28.89, 22.56 (–CH<sub>2</sub>), 14.44 (–CH<sub>3</sub>); IR (ν<sub>max</sub>, cm<sup>–1</sup>): 3094 ν(N–H), 1590 ν(C=N), 1029 ν(N–N), 918 ν(C=S).

[(2*E*)-2-[(Thiophen-2-yl)methylidene]hydrazine-1-carbothioamide] (**15**, **41**), (**4**). Pale yellow crystals; mp 209–211°C; Anal. Calc for C<sub>6</sub>H<sub>7</sub>N<sub>3</sub>S<sub>2</sub>: C 38.90, H 3.81, N 22.68%. Found: C 39.11, H 3.81, N 22.84%; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), δH: 11.50 (s, 1H, –NH), 8.25 (s, 1H, –CH=N), 7.55 & 8.22 2x(br, 1H, –NH<sub>2</sub>), 7.65 (d, 1H), 7.45 (d, 1H), 7.12 (t, 1H) (thiophene-3H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>), δC: 177.97 (–C=S), 139.07 (–CH=N), 138.07, 131.07, 129.34, 128.40 (heterocyclic carbons); IR (ν<sub>max</sub>, cm<sup>–1</sup>): 3410, 3231, 3132 ν(N–H), 1578 ν(C=N), 1099 ν(N–N), 939 ν(C=S); EI-MS Calc. for C<sub>6</sub>H<sub>7</sub>N<sub>3</sub>S<sub>2</sub> [M]<sup>+</sup>: 185.26, Found: 185.

[Methyl (2*E*)-2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbodithioate] (**42**), (**5**). Yellow solids; mp 194–196°C; Anal. Calc for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>OS<sub>2</sub>: C 47.77, H 4.45, N 12.38%. Found: C 47.96, H 4.39, N 12.41%; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), δH: 13.35 (s, 1H, –NH), 10.30 (s, 1H, –OH), 8.55 (s, 1H, –CH=N), 7.68 (d, 1H), 7.30 (t, 1H), 6.92 (d, 1H), 6.90 (t, 1H) (Ar-H), 2.51 (s, 3H, –SCH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>), δC: 197.73 (–C=S), 157.69 (phenolic carbon), 144.98 (–CH=N), 133.72, 127.69, 120.09, 119.55, 116.86 (aromatic carbons), 17.23 (–SCH<sub>3</sub>); IR (ν<sub>max</sub>, cm<sup>–1</sup>): 3467 ν(O–H), 3103 ν(N–H), 1603 ν(C=N), 1042 ν(N–N), 962 ν(C=S); EI-MS Calc. for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>OS<sub>2</sub> [M]<sup>+</sup>: 226.31, Found: 226.

[Benzyl (2*E*)-2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbodithioate] (**43**, **44**), (**6**). Pale yellow solids; mp 183–185°C; Anal. Calc for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>OS<sub>2</sub>: C 59.58, H 4.67, N 9.26%. Found: C 59.35, H 4.28, N 9.15%; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), δH: 13.38 (s, 1H, –NH), 10.23 (s, 1H, –OH), 8.53 (s, 1H, –CH=N), 7.65 (d, 1H), 7.26 (m, 1H), 7.28 (m, 1H), 6.93 (d, 1H), 7.45 (d, 2H), 7.35 (t, 2H), 6.85 (t, 1H) (Ar-H), 4.50 (s, 2H, –SCH<sub>2</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>), δC: 195.93 (–C=S), 157.70 (phenolic carbon), 145.02 (CH=N), 137.23, 132.76, 129.72, 128.98, 127.73, 127.49, 120.08, 119.56, 116.83 (aromatic carbons), 38.01 (–SCH<sub>2</sub>); IR (ν<sub>max</sub>, cm<sup>–1</sup>): 3375 ν(O–H), 3100 ν(N–H), 1605 ν(C=N), 1042 ν(N–N), 951 ν(C=S); EI-MS Calc. for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>OS<sub>2</sub> [M]<sup>+</sup>: 302.41, Found: 302.

[Octyl (2*E*)-2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbodithioate], (**7**). Yellowish-white solid; mp 82–83°C; Anal. Calc for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>OS<sub>2</sub>: C 59.22, H 7.45, N 8.63%. Found: C 59.45, H 7.24, N 8.59%; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), δH: 13.28 (s, 1H, –NH), 10.50 (s, 1H, –OH),



8.50 (s, 1H,  $-\text{CH}=\text{N}$ ), 7.60 (d, 1H), 7.33 (t, 1H), 6.93 (d, 1H), 6.92 (t, 1H) (Ar-H), 3.20 (t, 2H,  $-\text{SCH}_2$ ), 1.65 (quint, 2H), 1.40 (m, 8H), 1.35 (m, 2H) ( $-\text{CH}_2$ ), 0.80 (t, 3H,  $-\text{CH}_3$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta\text{C}$ : 196.82 ( $-\text{C}=\text{S}$ ), 157.51 (phenolic carbon), 144.70 ( $-\text{CH}=\text{N}$ ), 132.92, 127.80, 120.37, 119.30, 116.87 (aromatic carbons), 33.54 ( $-\text{SCH}_2$ ), 31.53, 28.82, 28.68, 28.56, 22.44 ( $-\text{CH}_2$ ), 14.34 ( $-\text{CH}_3$ ); IR ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ ): 3229  $\nu(\text{O}-\text{H})$ , 3109  $\nu(\text{N}-\text{H})$ , 1618  $\nu(\text{C}=\text{N})$ , 1024  $\nu(\text{N}-\text{N})$ , 947  $\nu(\text{C}=\text{S})$ ; EI-MS Calc. for  $\text{C}_{16}\text{H}_{24}\text{N}_2\text{OS}_2$   $[\text{M}]^{+\bullet}$ : 324.50, Found: 324.

[(2E)-2-[(2-Hydroxyphenyl)methylidene]hydrazine-1-carbothioamide] (**45**), (**8**). Brown solids; mp 247–249°C; Anal. Calc for  $\text{C}_8\text{H}_9\text{N}_3\text{OS}$ : C 49.22, H 4.65, N 21.52%. Found: C 48.96, H 4.55, N 21.34%;  $^1\text{H}$  NMR (DMSO- $d_6$ ),  $\delta\text{H}$ : 11.50 (s, 1H,  $-\text{NH}$ ), 9.95 (s, 1H,  $-\text{OH}$ ), 8.50 (s, 1H,  $-\text{CH}=\text{N}$ ), 8.16 & 7.95 2x(s, 1H,  $-\text{NH}_2$ ), 7.93 (m, 1H), 7.23 (t, 1H), 6.82 (t, 1H), 6.85 (d, 1H) (Ar-H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ),  $\delta\text{C}$ : 178.07 ( $-\text{C}=\text{S}$ ), 156.85 (phenolic carbon), 140.01 ( $-\text{CH}=\text{N}$ ), 131.55, 127.18, 120.80, 119.72, 116.47 (aromatic carbons); IR ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ ): 3422  $\nu(\text{O}-\text{H})$ , 3310, 3171, 3130  $\nu(\text{N}-\text{H})$ , 1599  $\nu(\text{C}=\text{N})$ , 1063  $\nu(\text{N}-\text{N})$ , 947  $\nu(\text{C}=\text{S})$ ; EI-MS Calc. for  $\text{C}_8\text{H}_9\text{N}_3\text{OS}$   $[\text{M}]^{+\bullet}$ : 195.24, Found: 195.

### Single Crystal X-ray structure analysis

X-ray crystallographic data for Schiff base **1** was collected by selecting a suitable crystal and was attached to a MiTeGen loop with Apiezon grease on a Rigaku Mercury375R (2 × 2 bin mode) diffractometer. The crystal was kept at 223 K during data collection. Using Olex2 (**46**), the structure was solved with the SIR2004 (**47**) structure solution program using Direct Methods and refined with the olex2.refine (**48**) refinement package using Gauss-Newton minimization.

X-ray crystallographic data for Schiff bases **3** and **4** were collected with on a Bruker AXS D8 Venture using a Mo-K $\alpha$  monochromatized ( $\lambda = 0.71073 \text{ \AA}$ ) X-ray radiation. Frames were integrated with SAINT software package (**49**) and data were corrected for absorption effects using the multi-scan method implanted in the SADABS software (**50**). The structures were solved by direct methods (**51**) and subsequently completed by Fourier recycling and refined by the full-matrix least squares refinements based on  $F^2$  using SHELXL (**52**) included in WinGx system programs for Windows (**53**). All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were allowed to ride their parent atoms with ideal geometries. All the hydrogen atoms were introduced as fixed contributors for the final cycle of least-squares refinement and they were refined isotropically.

Their selected bond lengths and bond angles are within the expected range and normal values (Tables S1, S2 and S3). Crystallographic data (excluding structure

factors) for compounds **1**, **3** and **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC. 1893124, 1893125 and 1893127 respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail:deposit@ccdc.cam.ac.uk).

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### Disclosure statement

No potential conflict of interest was reported by the author(s).

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