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Syntheses and evaluation of antioxidant activity of sydnonyl substituted thiazolidinone and thiazoline derivatives

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Abstract—3-Aryl-4-formylsydnone 4′-phenylthiosemicarbazones (**3a–d**) and 3-aryl-4-formylsydnone thiosemicarbazones (**3e–h**), which are precursors of 3-aryl-4-heterocyclic sydnones, are prepared by the condensation of 3-aryl-4-formylsydnones (**1a–d**) with 4′-phenylthiosemicarbazide (**2a**) and thiosemicarbazide (**2b**), respectively. The thiosemicarbazones **3** reacted with cyclic reagents such as ethyl chloroacetate (**4a**), ethyl 2-chloroacetoacetate (**4b**) and 2-bromoacetophenone (**4c**) to produce heterocyclic substituted sydnone derivatives **5–7** that possess 4-oxo-thiazolidine and thiazoline groups. The antioxidant activity of synthesized compounds **5a–7h** was evaluated. Among these compounds, 4-methyl-2-[(3-arylsydnon-4-yl-methylene)hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (**6e–h**) and 4-phenyl-2-[(3-arylsydnon-4-yl-methylene)hydrazono]-2,3-dihydro-thiazoles (**7e–h**) exhibit the potent DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity, comparable to that of vitamin E.

1. Introduction

Several sydnone derivatives have associated with a broad range of physiological activities, exhibiting antimicrobial, anti-inflammatory, analgesic and antipyretic properties.[1–3] Hence, chemists have been enthusiastically pursuing the syntheses of these derivatives.[4–6] Thiosemicarbazones have been reported to exhibit antituberculosis activity.[7,8] Besides, thiazoles and their derivatives exhibit various biological activities such as antimicrobial, anti-inflammatory, antiviral, antituberculosis and cytotoxic activities, among others.[9–18] Following reports of these activities, this study seeks to synthesize a series of novel thiazole derivatives that contain the sydnonyl moiety, with the aim of obtaining new biologically active compounds. In view of the continued interest in the development of simpler and more convenient synthetic routes for preparing heterocyclic systems,[19–27] an efficient and useful method is reported herein to synthesize some new sydnonyl-substituted thiazolidinones and thiazolines by the reaction of 3-aryl-4-formylsydnone 4′-phenylthiosemicarbazones (**3a–d**) or 3-aryl-4-formylsydnone thiosemicarbazones (**3e–h**) with cyclic reagents such as ethyl chloroacetate (**4a**), ethyl 2-chloroacetoacetate **4b** and 2-bromoacetophenone (**4c**). The scavenging effects of all of the synthesized compounds on the DPPH free radical are evaluated. Nowadays, antioxidants that exhibit DPPH radical scavenging activity are increasingly receiving attention. They have been reported to have interesting anticancer, antiageing and anti-inflammatory activities. To the authors' knowledge, no investigation of the radical scavenging effects of synthesized sydnone derivatives has yet been undertaken. Accordingly, a study of the syntheses of new sydnone derivatives with antioxidant activity would support the development of new drugs and improve the treatment of various diseases.

2. Results and discussion

2.1. Synthetic chemistry

Thiosemicarbazones exhibit various biological activities and are widely used in medicine, especially in the treatment of tuberculosis.[7,8] Many compounds with a thiosemicarbazone moiety also exhibit biological

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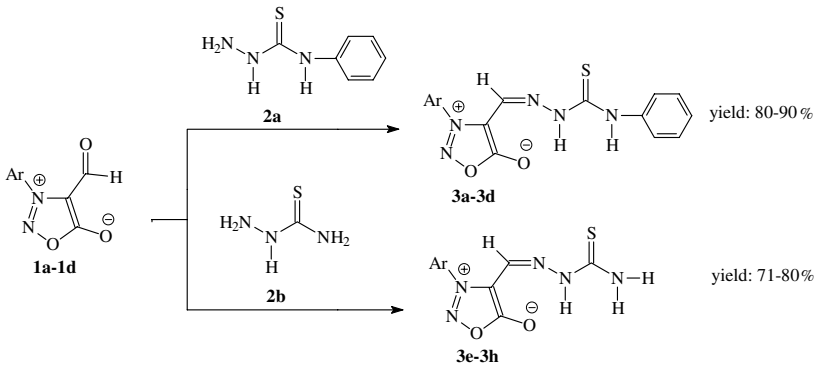
activity.[28] Accordingly, 3-aryl-4-formylsydnone 4′-phenylthiosemicarbazones (**3a**–**d**) and 3-aryl-4-formylsydnone thiosemicarbazones (**3e**–**h**) were synthesized in good yields by the reactions of 3-aryl-4-formylsydnones (**1a**–**d**) with 4′-phenylthiosemicarbazide (**2a**) and thiosemicarbazide (**2b**), respectively (Scheme 1).

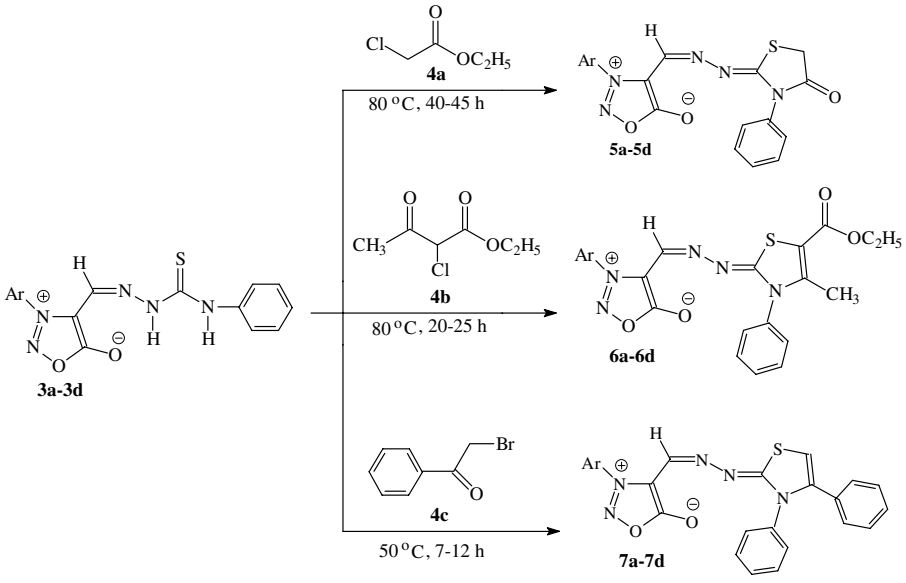
Thiazolidine-4-ones are well known for their pharmacological activities. Several substituted thiazolidinones have been found to possess hypnotic, anaesthetic, sedative, anticonvulsant and microbiological activities.[29–31] In view of the various physiological activities of thiazolidinone derivatives, many thiazolidinone derivatives have been prepared. In this report, 3-aryl-4-formylsydnone 4′-phenyl thiosemicarbazones (**3a**–**d**) were used to react with ethyl chloroacetate (**4a**) in ethanol solution that contained sodium acetate/acetic acid buffer system, to produce 2-[(3-aryl-sydnon-4-ylmethylene)hydrazono]-3-phenyl-thiazolidin-4-ones (**5a**–**d**) in high yields (Scheme 2).

The sydnone ring is sensitive to acids such as hydrochloric acid, and sydnone compounds are sometimes decomposed during reaction and/or workup, so in the reaction, sodium acetate was used to scavenge the released hydrogen chloride that could cause the decomposition of sydnones. Acetic acid was used to catalyze the cyclization. Increasing the amount of acetic acid accelerated the reaction. Besides, acetic acid and sodium acetate form a buffer system to maintain the pH value of the reaction solution at 4.6–4.7 and avoid the decomposition of sydnones. Therefore, under optimal conditions, compounds **3a**–**d** reacted with ethyl chloroacetate in ethanol solution with a catalytic amount of acetic acid to yield the desired products **5a**–**d**. All these products were spectroscopically characterized. Among the new products **5a**–**d**, the orange crystal **5c** was analytically pure and suitable for X-ray structure analyses. Figure 1 presents the molecular structure of compound **5c**.

The pharmacological properties of thiazolines have been studied. Thus, some thiazoline derivatives show interesting anti-HIV or anticancer activities and can inhibit cell division.[32–34] This paper presents a convenient strategy for synthesizing 4-methyl-5-ester-substituted thiazolines **6** and 4-phenyl-substituted thiazolines **7**. Cyclic reagents



Scheme 1. **1a**: Ar = C_6H_5; **1b**: Ar = *p*-$CH_3C_6H_4$; **1c**: Ar = *p*-$CH_3OC_6H_4$; **1d**: Ar = *p*-$C_2H_5OC_6H_4$.



Scheme 2. **3a**: Ar = C_6H_5; **3b**: Ar = *p*-$CH_3C_6H_4$; **3c**: Ar = *p*-$CH_3OC_6H_4$; **3d** : Ar = *p*-$C_2H_5OC_6H_4$.

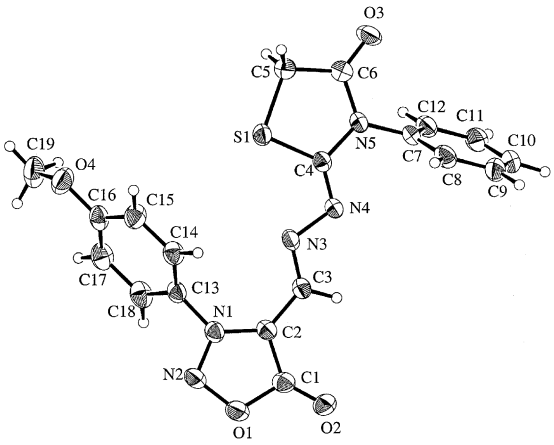


Figure 1. Crystal structure of compound **5c**.

such as ethyl 2-chloroacetoacetate (**4b**) and 2-bromoacetophenone (**4c**) were allowed to react with 3-aryl-4-formylsydnone 4′-phenylthiosemicarbazones (**3a**–**d**) in buffer systems of sodium acetate and acetic acid, to produce the desired products 2-[(3-arylsydnon-4-ylmethylene)hydrazono]-4-methyl-3-phenyl-2,3-dihydro-thiazole-5-carboxylic acid ethyl esters (**6a**–**d**) and 3,4-diphenyl-2-[(3-arylsydnon-4-ylmethylene)hydrazono]-2,3-dihydrothiazoles (**7a**–**d**) in good yields, too (Scheme 2).

All the reactions of compounds **3a**–**d** with reagents **4a**–**c** were initiated at room temperature and then heated until completion. The reaction time and reaction temperature of these cyclic reagents **4a**–**c** with compounds **3** imply that the order of their reactivities is **4c** > **4b** > **4a**. All these products were spectroscopically characterized. Among these new thiazoline derivatives **6a**–**7d**, the orange crystals **6b** and **7c** were analytically pure and suitable for X-ray structure analyses. Figures 2 and 3 show the molecular structures of compounds **6b** and **7c**. Details of crystal data of compounds **5c**, **6b** and **7c** are given in Table 1.

Treatment of 3-aryl-4-formylsydnone thiosemicarbazones (**3e**–**h**) with reagents **4a**–**c** in ethanol solution that contains sodium acetate and acetic acid buffer systems yielded the desired products **5e**–**h**, **6e**–**h** and **7e**–**h** also in good yields (Scheme 3). The reaction time, the reaction temperature and the corresponding yields of the reaction **3a**–**h** with reagents **4a**–**c** imply that compounds **3e**–**h** are more reactive than compounds **3a**–**d**, because the steric effect of the phenyl group reduces the ability of compounds **3a**–**d** to undergo nucleophilic cyclization, and the greater electron density on the NH_2 in compounds **3e**–**h** than on the NH in compounds **3a**–**d** increases the ability of compounds **3e**–**h** to undergo nucleophilic cyclization.

Among the cyclic reagents **4a**–**c**, 2-bromoacetophenone (**4c**) is the most reactive compound with thiosemicarbazones **3**. The reactions of **4c** with **3e**–**h** must be performed in an ice-cooled system to prevent the decomposition of sydnone compounds during the reaction. The reactions were initially also controlled by the successive addition of reagent **4c**, sydnones, sodium acetate and acetic acid in that order, but still, the starting materials **3e**–**h** were unavoidably decomposed. Many tests established that sodium acetate and acetic acid should be first added to the ice-cooled solution of sydnone **3**. Then, cyclic reagent **4c** was slowly added to the buffer solution and the mixture was stirred to precipitate the desired material. Consequently, under optimal experimental conditions, compounds **3e**–**h** reacted with 2-bromoacetophenone (**4c**) in ethanol to generate products **7e**–**h** in high yields (Scheme 3).

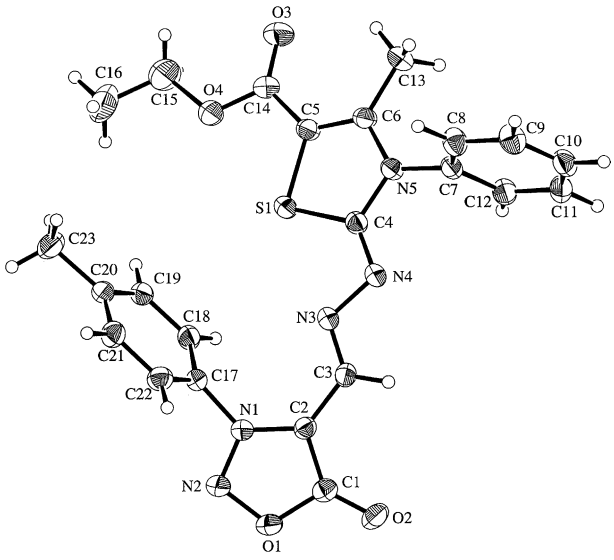


Figure 2. Crystal structure of compound **6b**.

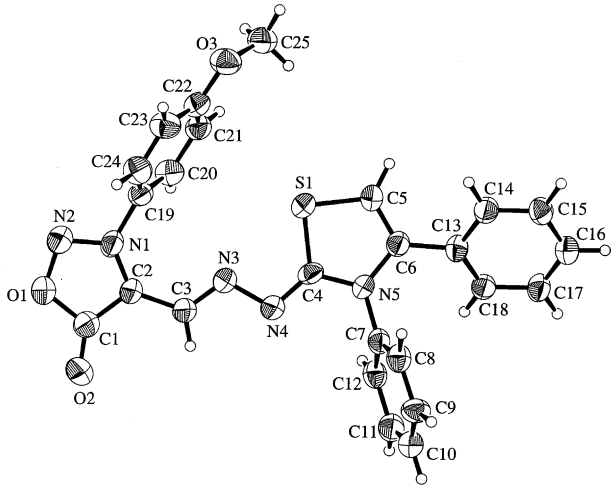


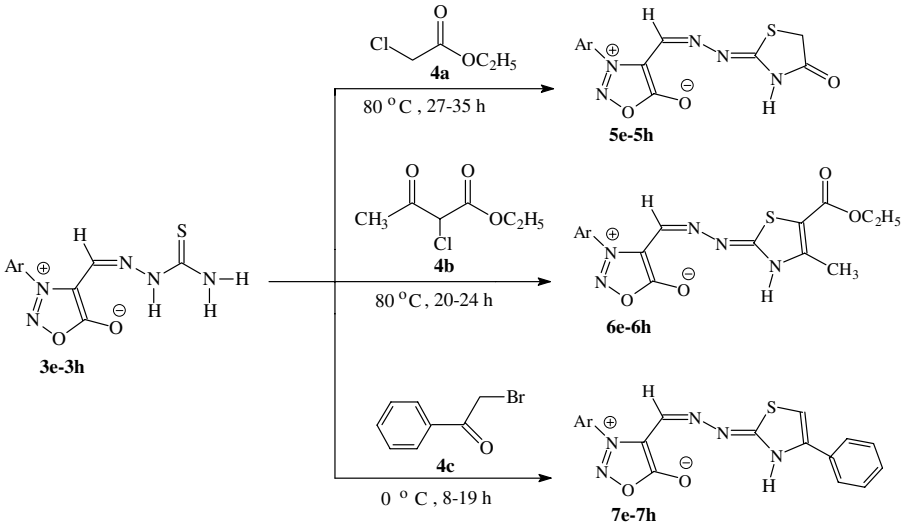
Figure 3. Crystal structure of compound **7c**.

2.2. Scavenging effect of antioxidant activity on DPPH radical

The model of the scavenging of the stable DPPH radical is extensively used to evaluate antioxidant activities in less time than other methods. DPPH is a stable free radical that can accept an electron or hydrogen radical and thus be converted into a stable, diamagnetic molecule. DPPH has an odd electron and so has a strong absorption band at 517 nm. When this electron becomes paired

Table 1. Crystal data of compounds **5c**, **6b** and **7c**

Compound	**5c**	**6b**	**7c**
Diffractometer	Rigaku AFC7S	Rigaku AFC7S	Rigaku AFC7S
Formula	$C_{19}H_{15}N_5O_4S$	$C_{23}H_{21}N_5O_4S$	$C_{25}H_{19}N_5O_3S$
Formula weight	409.42	463.51	469.52
Crystal system	Monoclinic	Triclinic	Orthorhombic
Crystal colour, habit	Orange, plate	Orange, prism	Red, prism
Space group	*Cc* (#9)	*P*1̄(#2)	$Pca2_1$ (#29)
a (Å)	24.775(4)	10.165(2)	24.48(1)
b (Å)	5.325(4)	12.394(2)	5.593(4)
c (Å)	14.157(6)	10.026(2)	16.52(1)
α (°)		90.97(1)	
β (°)	97.17(2)	110.47(1)	
γ (°)		73.86(1)	
V (Å^3)	1853(1)	1132.2(3)	2262(2)
Z	4	2	4
D_{calc} (g cm^{-3})	1.467	1.360	1.378
F_{000}	848.00	484.00	976.00
μ (Mo K$_\alpha$) (cm^{-1})	2.13	1.83	1.82
Crystal size (mm)	0.20×0.60×0.80	0.20×0.60×0.70	0.35×0.55×0.65
Temperature (K)	293	293	293
Scan type	*ω*–2*θ*	*ω*–2*θ*	*ω*–2*θ*
$2\theta_{max}$ (°)	52.0	52.0	52.1
Reflections measured	2087	4722	2592
Unique reflections	2035 (R_{int} = 0.015)	4457 (R_{int} = 0.017)	
No. observations [$I > 3.00\sigma(I)$]	1451	3218	1281
No. variables	262	298	307
Residuals: *R*; *Rw*	0.039; 0.057	0.044; 0.064	0.060; 0.082
GoF	1.53	1.82	1.82



Scheme 3. **3e**: Ar = C_6H_5; **3f**: Ar = *p*-$CH_3C_6H_4$; **3g**: Ar = *p*-$CH_3OC_6H_4$; **3h**: Ar = *p*-$C_2H_5OC_6H_4$.

off, the absorption decreases stoichiometrically with respect to the number of electrons taken up. Such a change in the absorbance produced in this reaction has been widely applied to test the capacity of numerous molecules to act as free radical scavengers. The scavenging effect of the synthesized compounds **5a**–**7h** on the DPPH radical was evaluated according to the methods of Shimada et al.,[35] Leong and Shui[36] and Braca et al.[37] Various concentrations of the test compound in 1.5 mL methanol were added to a 1.5 mL (0.2 mM) solution of DPPH radical in methanol (final concentration of DPPH was 0.1 mM). The mixture was shaken vigorously and allowed to stand for 30 min or more; absorbance at 517 nm was determined by a Hitachi U-2001 spectrophotometer, and the percentage of activity was calculated. Vitamin E was used as a reference compound. All tests and analyses were undertaken on three replicates and the results averaged. The tests reveal that the reaction with DPPH is in a time-dependent fashion and that the more the concentration of the tested compound the higher the radical scavenging activity it is. However, compounds **5a**–**h** with 4-oxo-thiazolidine moiety exhibited 50–60% radical scavenging activity after standing 3 h (10–20% in 30 min) at a final concentration

of 0.1 mM. Compounds **6a–d** and **7a–d** with 3-phenyl-2,3-dihydrothiazole moiety showed 10–15% and 0–5% radical scavenging activity (in 30 min incubation), respectively. In contrast, compounds **6e–h** and **7e–h** with 2,3-dihydrothiazole moiety scavenge DPPH radical very fast and the incubated time only takes 10 min to reach equilibrium. Compounds **6e–h** and **7e–h** exhibited very good radical scavenging activity 90–98% at a final concentration of 0.1 mM. The radical scavenging effects for each of the compounds **5a–7h** (0.1 mM) incubated 30 min with DPPH at 0.1 mM concentration are shown in Figure 4. The profiles of the scavenging effect of compounds **6e–h** and **7e–h** on DPPH are comparable to that of vitamin E, and are presented in Figures 5 and 6, respectively. In this study, compounds **6e–h** and **7e–h** exhibited strong activity, perhaps due to the presence of the functional group N–H in the 2,3-dihydrothiazole moiety, which can donate hydrogen atoms. After donating a hydrogen atom, compounds **6e–h** and **7e–h** with 2,3-dihydrothiazole moiety exist in radical form, and the electron conjugation effect in the structure stabilizes the radical so that it does not become involved in a destructive biochemical reaction.

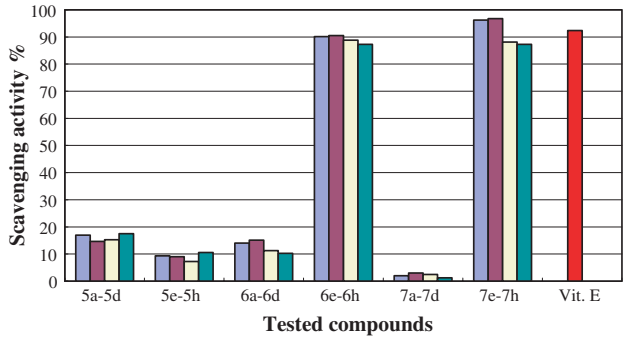


Figure 4. Scavenging activity of compounds **5a–7h** (0.1 mM) incubated 30 min with DPPH at 0.1 mM concentration.

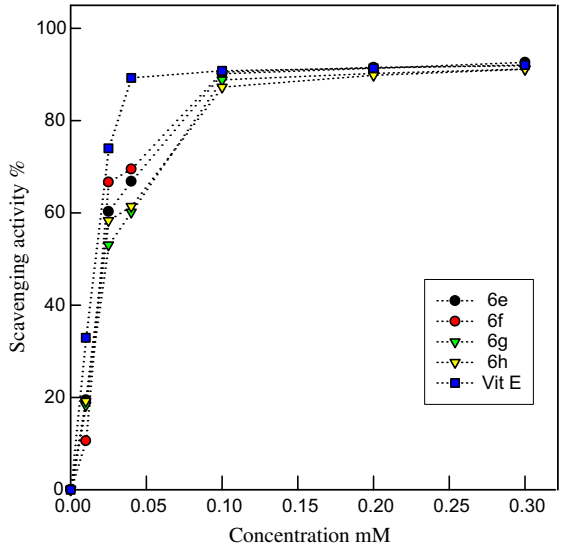


Figure 5. Scavenging activity of compounds **6e–h** on DPPH radical.

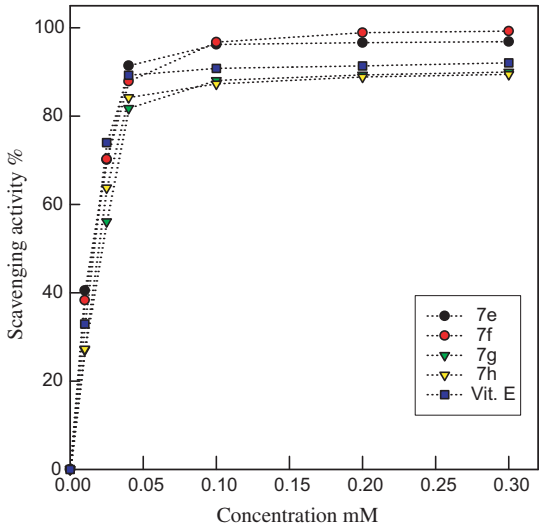


Figure 6. Scavenging activity of compounds **7e–h** on DPPH radical.

3. Conclusion

In summary, various biologically active compounds that contain a thiazolindinone or thiazoline moiety have been discovered or chemically synthesized. This work describes an efficient method of obtaining sydnonyl-substituted thiazolindinones or thiazolines. Applying this method to the cyclization of 3-aryl-4-formylsydnone 4′-phenylthiosemicarbazones (**3a–d**) or 3-aryl-4-formylsydnone thiosemicarbazones (**3e–h**) with ethyl chloroacetate (**4a**), ethyl 2-chloroacetoacetate (**4b**) and 2-bromoacetophenone (**4c**) provides access to the target compounds, such as thiazolidin-4-ones **5a–h**, 4-methyl-2,3-dihydro-thiazole-5-carboxylic acid ethyl esters **6a–h** and 4-phenyl-2,3-dihydro-thiazoles **7a–h**. Among these, compounds **6e–h**, **7e–h** exhibit a potent DPPH radical scavenging activity, which is comparable to that of vitamin E. The 2,3-dihydrothiazole moiety of compounds **6e–h** and **7e–h** plays an important role in the scavenging radical activity.

4. Experimental

4.1. General

All melting points were determined on an England Electrothermal Digital Melting Point apparatus and are uncorrected. IR spectra were recorded on a MATTSON/SATELLITE 5000 FT-IR spectrophotometer. Mass spectra were measured on a VG Quattro GC/MS/MS/DS spectrometer. ^{1}H NMR spectra were run on a Bruker AMX-200 NMR spectrometer, using TMS as an internal standard. ^{13}C NMR spectra were carried out with complete ^{1}H decoupling and assignments were made through additional DEPT experiments. Elemental analyses were taken with a Heraeus CHN-O-Rapid Analyzer or Elementar Vario EL-III Analyzer. X-ray spectra were performed on a Rigaku AFC7S diffractometer. 3-Phenyl-4-formylsydnone (**1a**), 3-(4-methylphenyl)-4-formylsydnone (**1b**), 3-(4-methoxyphenyl)-4-formylsydnone (**1c**) and 3-(4-ethoxyphenyl)-4-

formylsydnone (**1d**) were prepared according to the literature.[19]

4.2. Syntheses of 3-aryl-4-formylsydnone 4′-phenyl thiosemicarbazones (3a–d)

To a solution of 3-phenyl-4-formylsydnone (**1a**, 570 mg, 3.0 mmol) in absolute ethanol (20 mL), 4-phenylthiosemicarbazide (**2a**, 526 mg, 3.15 mmol) was slowly added. The mixed solution was heated at 45 °C for 2–3 days and then cooled. The precipitating solid was collected by filtration and recrystallized from dichloromethane/ethanol to afford 815 mg (80%) of 3-phenyl-4-formylsydnone 4′-phenylthiosemicarbazone **3a** as yellow powder. The chemical and physical spectral characteristics of these products **3a**–**d** are given below.

4.2.1. 3-Phenyl-4-formylsydnone 4′-phenylthiosemicarbazone (3a). Yellow powder from CH_2Cl_2/EtOH; yield 80%; mp 170–171 °C; IR (KBr) 3322, 3148, 2986, 1776, 1590, 1533, 1515, 1260, 1203 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.14–7.89 (m, 11H), 8.66 (s, 1H), 11.93 (s, 1H); FABMS$^+$ *m/z* (%): 340 ($M^+ + H$, 100), 339 (M^+, 17); Anal. Calcd for $C_{16}H_{13}N_5O_2S$: C, 56.63; H, 3.86; N, 20.64. Found: C, 56.55; H, 3.84; N, 20.57.

4.2.2. 3-(4-Methylphenyl)-4-formylsydnone 4′-phenyl-thiosemicarbazone (3b). Yellow powder from CH_2Cl_2/EtOH; yield 83%; mp 177–178 °C; IR (KBr) 3286, 3224, 1743, 1599, 1543, 1515, 1257, 1194 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.22 (s, 3H), 7.13–7.39 (m, 5H), 7.48 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H), 7.84 (s, 1H), 8.40 (s, 1H), 11.96(s, 1H); FABMS$^+$ *m/z* (%): 354 ($M^+ + H$, 100), 353 (M^+, 18); Anal. Calcd for $C_{17}H_{15}N_5O_2S$: C, 57.78; H, 4.28; N, 19.82. Found: C, 57.66; H, 4.29; N, 19.84.

4.2.3. 3-(4-Methoxyphenyl)-4-formylsydnone 4′-phenylthiosemicarbazone (3c). Yellow needles from CH_2Cl_2/EtOH; yield 90%; mp 176–177 °C; IR (KBr) 3292, 3214, 3064, 1740, 1605, 1533, 1515, 1260, 1188 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.69 (s, 3H), 7.18–7.40 (m, 7H), 7.79 (d, J = 9.0 Hz, 2H), 7.84 (s, 1H), 8.57 (s, 1H), 11.95 (s, 1H); FABMS$^+$ *m/z* (%): 370 ($M^+ + H$, 100), 369 (M^+, 15); Anal. Calcd for $C_{17}H_{15}N_5O_3S$: C, 55.27; H, 4.09; N, 18.96. Found: C, 55.25; H, 4.09; N, 18.99.

4.2.4. 3-(4-Ethoxyphenyl)-4-formylsydnone 4′-phenyl-thiosemicarbazone (3d). Yellow needles from CH_2Cl_2/EtOH; yield 82%; mp 176–177 °C; IR (KBr) 3294, 3214, 3064, 2988, 2932, 1740, 1596, 1533, 1515, 1257, 1185 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.25 (t, J = 7.0 Hz, 3H), 3.90 (q, J = 7.0 Hz, 2H), 7.15–7.43 (m, 7H), 7.76 (d, J = 9.0 Hz, 2H), 7.83 (s, 1H), 8.49 (s, 1H), 11.95 (s, 1H); FABMS$^+$ *m/z* (%): 384 ($M^+ + H$, 100), 383 (M^+, 18); Anal. Calcd for $C_{18}H_{17}N_5O_3S$: C, 56.38; H, 4.47; N, 18.27. Found: C, 56.25; H, 4.43; N, 18.32.

4.3. Syntheses of 3-aryl-4-formylsydnone thiosemicarbazones (3e–h)

To a solution of 3-phenyl-4-formylsydnone (**1a**, 570 mg, 3.0 mmol) in absolute ethanol (20 mL), thiosemicarbazide (**2b**, 287 mg, 3.15 mmol) was slowly added. The mixed solution was heated at 45 °C for 2–3 days and then cooled. The precipitating solid was collected by filtration and recrystallized from dichloromethane/ethanol to afford 624 mg (79%) of 3-phenyl-4-formylsydnone thiosemicarbazone (**3e**) as yellow crystal. The chemical and physical spectral characteristics of these products **3e**–**h** are given below.

4.3.1. 3-Phenyl-4-formylsydnone thiosemicarbazone (3e). Yellow crystals from CH_2Cl_2/EtOH; yield 79%; mp 188–190 °C; IR (KBr) 3406, 3262, 3154, 1737, 1599, 1521, 1263 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.33 (s, 1H), 7.91–7.63 (m, 6H), 8.28 (s, 1H), 11.50 (s, 1H); FABMS$^+$ *m/z* (%): 264 ($M^+ + H$, 100), 263 (M^+, 19); Anal. Calcd for $C_{10}H_9N_5O_2S$: C, 45.62; H, 3.45; N, 26.60. Found: C, 45.51; H, 3.47; N, 26.53.

4.3.2. 3-(4-Methylphenyl)-4-formylsydnone thiosemicarbazone (3f). Yellow powder from CH_2Cl_2/EtOH; yield 71%; mp 190–192 °C; IR (KBr) 3430, 3310, 3178, 3040, 2998, 1755, 1605, 1539, 1263 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H), 6.34 (s, 1H), 7.51(d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.72 (s, 1H), 8.29 (s, 1H), 11.47 (s, 1H); FABMS$^+$ *m/z* (%): 278 ($M^+ + H$, 100), 277 (M^+, 17); Anal. Calcd for $C_{11}H_{11}N_5O_2S$: C, 47.64; H, 4.00; N, 25.25. Found: C, 47.50; H, 4.11; N, 25.11.

4.3.3. 3-(4-Methoxyphenyl)-4-formylsydnone thiosemicarbazone (3g). Yellow powder from CH_2Cl_2/EtOH; yield 80%; mp 197–198 °C; IR (KBr) 3422, 3346, 3166, 3010, 2842, 1749, 1605, 1590, 1524, 1263 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.86 (s, 3H), 6.48 (s, 1H), 7.22 (d, J = 9.1 Hz, 2H), 7.73 (s, 1H), 7.74 (d, J = 9.1 Hz, 2H), 8.32 (s, 1H), 11.49 (s, 1H); FABMS$^+$ *m/z* (%): 294 ($M^+ + H$, 100), 293 (M^+, 18); Anal. Calcd for $C_{11}H_{11}N_5O_3S$: C, 45.05; H, 3.78; N, 23.88. Found: C, 44.85; H, 3.80; N, 23.80.

4.3.4. 3-(4-Ethoxyphenyl)-4-formylsydnone thiosemicarbazone (3h). Yellow needles from CH_2Cl_2/EtOH; yield 78%; mp 191–192 °C; IR (KBr) 3394, 3232, 3154, 2988, 1734, 1593, 1527, 1254 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.36 (t, J = 7.1 Hz, 3H), 4.13 (q, J = 7.1 Hz, 2H), 6.47 (s, 1H), 7.20 (d, J = 8.9 Hz, 2H), 7.72 (d, J = 8.9 Hz, 2H), 7.73 (s, 1H), 8.33 (s, 1H), 11.47 (s, 1H); FABMS$^+$ *m/z* (%): 308 ($M^+ + H$, 100), 307 (M^+, 25); Anal. Calcd for $C_{12}H_{13}N_5O_3S$: C, 46.90; H, 4.26; N, 22.79. Found: C, 46.75; H, 4.26; N, 22.78.

4.4. Syntheses of 2-[(3-arylsydnon-4-ylmethylene) hydrazono]-3-phenyl-thiazolidin-4-ones (5a–d)

To a solution of ethyl chloroacetate (**4a**, 184 mg, 1.50 mmol) in absolute ethanol (5 mL), were slowly added 3-phenyl-4-formylsydnone 4′-phenylthiosemicarbazone (**3a**, 339 mg, 1.00 mmol) and sodium acetate (246 mg, 3.00 mmol). Acetic acid (0.5 mL) was added to the above solution as a catalyst. The mixed solution was heated to 80 °C for around 40 h until the reaction was completed. The system was then allowed to attain room temperature. The precipitated solid was collected by filtration and washed with ice-cold water

and cold ethanol. The collected solid was recrystallized from acetone/ethanol to yield 235 mg (62%) of 2-[(3-phenylsydnon-4-ylmethylene)hydrazono]-3-phenyl-thiazolidin-4-one (**5a**) as yellow powder. The chemical and physical spectral characteristics of these products **5a–d** are given below.

4.4.1. 2-[(3-Phenylsydnon-4-ylmethylene)hydrazono]-3-phenyl-thiazolidin-4-one (5a). Yellow powder from CH_3COCH_3/EtOH; yield 62%; mp 210–211 °C; IR (KBr) 3058, 2974, 1764, 1721, 1607, 1547, 1241 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.01 (s, 2H), 7.20–7.35 (m, 2H), 7.37–7.55 (m, 3H), 7.68 (s, 1H), 7.70–7.90 (m, 5H); ^{13}C NMR (DMSO-d_6): δ 32.56, 105.39, 125.72, 128.33, 128.94, 129.28, 130.24, 132.65, 133.87, 135.00, 142.52, 164.95, 166.77, 172.24; FABMS$^+$ *m/z* (%): 380 (M^+ + H, 100), 379 (M^+, 14), 349 (M^+–NO, 21), 321 (M^+–NO–CO, 27); Anal. Calcd for $C_{18}H_{13}N_5O_3S$: C, 56.99; H, 3.45; N, 18.46. Found: C, 57.00; H, 3.46; N, 18.47.

4.4.2. 2-{[3-(4-Methylphenyl)sydnon-4-ylmethylene]-hydrazono}-3-phenyl-thiazolidin-4-one (5b). Yellow powder from CH_3COCH_3/EtOH; yield 68%; mp 202–203 °C; IR (KBr) 3057, 2980, 1761, 1717, 1606, 1547, 1243 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.41 (s, 3H), 4.03 (s, 2H), 7.16–7.49 (m, 7H), 7.62 (s, 1H), 7.66 (d, J = 8.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 21.10, 32.53, 105.33, 125.41, 128.28, 128.85, 129.20, 130.54, 131.18, 134.99, 142.67, 142.89, 164.61, 166.60, 172.17; FABMS$^+$ *m/z* (%): 394 (M^+ + H, 100), 393 (M^+, 15), 363 (M^+–NO, 17), 335 (M^+–NO–CO, 22); Anal. Calcd for $C_{19}H_{15}N_5O_3S$: C, 58.01; H, 3.84; N, 17.80. Found: C, 58.00; H, 3.98; N, 17.54.

4.4.3. 2-{[3-(4-Methoxyphenyl)sydnon-4-ylmethylene]-hydrazono}-3-phenyl-thiazolidin-4-one (5c). Orange crystals from CH_3COCH_3/EtOH; yield 58%; mp 203–204 °C; IR (KBr) 3054, 2977, 1757, 1717, 1610, 1550, 1252 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.84 (s, 3H), 4.03 (s, 2H), 7.19 (d, J = 9.0 Hz, 2H), 7.26–7.32 (m, 2H), 7.34–7.57 (m, 3H), 7.62 (s, 1H), 7.72 (d, J = 9.0 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 32.58, 56,05, 105.43, 115.30, 126.21, 127.24, 128.34, 128.94, 129.29, 135.04, 142.87, 162.12, 164.72, 166.60, 172.25; FABMS$^+$ *m/z* (%): 410 (M^+ + H, 100), 409 (M^+, 14), 379 (M^+–NO, 19), 351 (M^+–NO–CO, 25); Anal. Calcd for $C_{19}H_{15}N_5O_4S$: C, 55.74; H, 3.69; N, 17.11. Found: C, 55.76; H, 3.73; N, 17.11. X-ray analytical data are listed in Table 1. Further details have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 216222.

4.4.4. 2-{[3-(4-Ethoxyphenyl)sydnon-4-ylmethylene]-hydrazono}-3-phenyl-thiazolidin-4-one (5d). Yellow crystals from CH_3COCH_3/EtOH; yield 52%; mp 204–205 °C; IR (KBr) 3055, 2980, 1754, 1716, 1609, 1551, 1249 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.34 (t, J = 7.1 Hz, 3H), 4.04 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 7.15 (d, J = 9.0 Hz, 2H), 7.27–7.31 (m, 2H), 7.39–7.50 (m, 3H), 7.63 (s, 1H), 7.69 (d, J = 9.0 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 14.60, 32.53, 64.05, 105.37, 115.59, 125.99, 127.19, 128.30, 128.87, 129.22, 135.00, 142.84, 161.36, 164.66, 166.52, 172.18; FABMS$^+$ *m/z* (%): 424 (M^+ + H, 100), 423 (M^+, 10), 393 (M^+–NO, 17), 365 (M^+–NO–CO, 32); Anal. Calcd for $C_{20}H_{17}N_5O_4S$: C, 56.73; H, 4.05; N, 16.54. Found: C, 56.53; H, 4.08; N, 16.41.

4.5. Syntheses of 2-[(3-arylsydnon-4-ylmethylene)hydrazono]-4-methyl-3-phenyl-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6a–d)

To a solution of ethyl 2-chloroacetoacetate (**4b**, 247 mg, 1.50 mmol) in absolute ethanol (4 mL), 3-phenyl-4-formylsydnone 4′-phenylthiosemicarbazone (**3a**, 339 mg, 1.00 mmol) and sodium acetate (246 mg, 3.00 mmol) were slowly added. Acetic acid (0.5 mL) was added to the above solution as a catalyst. The mixed solution was heated at 80 °C for about 20 h and then allowed to attain room temperature. The precipitating solid was collected by filtration and washed with ice-cold water and cold ethanol. The collected solid was recrystallized from acetone/ethanol to yield 211 mg (47%) of 4-methyl-3-phenyl-2-[(3-phenylsydnon-4-ylmethylene)hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (**6a**) as yellow crystalline. The chemical and physical spectral characteristics of these products **6a–d** are given below.

4.5.1. 4-Methyl-3-phenyl-2-[(3-phenylsydnon-4-ylmethylene)hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6a). Yellow crystals from CH_3COCH_3/EtOH; yield 47%; mp 223–224 °C; IR (KBr) 3074, 2976, 1752, 1694, 1594, 1523, 1491, 1305, 1248 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.30 (t, J = 7.1 Hz, 3H), 2.13 (s, 3H), 4.24 (q, J = 7.1 Hz, 2H), 7.30–7.60 (m, 6H), 7.62–7.82 (m, 5H); ^{13}C NMR (DMSO-d_6): δ 13.86, 14.42, 60.91, 103.70, 106.07, 125.66, 128.70, 129.63, 129.87, 130.23, 132.39, 134.01, 135.84, 137.59, 147.38, 161.40, 164.86, 168.85; FABMS$^+$ *m/z* (%): 450 (M^+ + H, 100), 449 (M^+, 32), 419 (M^+–NO, 59); Anal. Calcd for $C_{22}H_{19}N_5O_4S$: C, 58.79; H, 4.26; N, 15.58. Found: C, 58.82; H, 4.39; N, 15.63.

4.5.2. 4-Methyl-3-phenyl-2-{[3-(4-methylphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6b). Orange crystals from CH_3COCH_3/EtOH; yield 40%; mp 240–241 °C; IR (KBr) 3074, 2975, 1762, 1707, 1601, 1523, 1492, 1304, 1260 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.28 (t, J = 7.2 Hz, 3H), 2.13 (s, 3H), 2.42 (s, 3H), 4.24 (q, J = 7.2 Hz, 2H), 7.30–7.56 (m, 8H), 7.63 (d, J = 8.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 13.97, 14.53, 21.14, 60.96, 103.67, 106.03, 125.40, 128.75, 129.68, 129.92, 130.60, 131.49, 135.92, 137.81, 142.75, 147.49, 161.49, 164.90, 168.67; FABMS$^+$ *m/z* (%): 464 (M^+ + H, 100), 463 (M^+, 25), 433 (M^+–NO, 47); Anal. Calcd for $C_{23}H_{21}N_5O_4S$: C, 59.60; H, 4.57; N, 15.11. Found: C, 59.65; H, 4.64; N, 15.15. X-ray analytical data are listed in Table 1. Further details have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 216223.

4.5.3. 4-Methyl-3-phenyl-2-{[3-(4-methoxyphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6c). Orange crystals from CH_3COCH_3/EtOH; yield 45%; mp 220–221 °C; IR (KBr) 3068, 2978, 1761, 1693, 1593, 1522, 1493, 1303, 1250 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.28 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 3.85 (s, 3H), 4.24 (q, J = 7.1 Hz, 2H), 7.18 (d, J = 9.1 Hz, 2H), 7.25–7.60 (m, 6H), 7.69 (d, J = 9.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 13.95, 14.45, 56.00, 60.96, 103.67, 106.09, 115.30, 126.40, 127.18, 128.76, 129.69, 129.94, 135.92, 138.05, 147.47, 161.51, 162.04, 164.86, 168.62; FABMS$^+$ m/z (%): 480 (M^+ + H, 100), 479 (M^+, 30), 449 (M^+–NO, 40); Anal. Calcd for $C_{23}H_{21}N_5O_5S$: C, 57.61; H, 4.41; N, 14.60. Found: C, 57.66; H, 4.44; N, 14.63.

4.5.4. 4-Methyl-3-phenyl-2-{[3-(4-ethoxyphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6d). Yellow powder from CH_3COCH_3/EtOH; yield 42%; mp 232-233 °C; IR (KBr) 3070, 2994, 1762, 1686, 1592, 1510, 1475, 1370, 1315 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.28 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.0 Hz, 3H), 2.15 (s, 3H), 4.12 (q, J = 7.0 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 7.16 (d, J = 9.1 Hz, 2H), 7.37–7.53 (m, 6H); 7.68 (d, J = 9.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 13.91, 14.40, 14.59, 60.88, 64.01, 103.61, 106.03, 115.58, 126.15, 127.14, 128.72, 129.62, 129.87, 135.88, 138.08, 147.40, 161.30, 161.44, 164.73, 168.52; FABMS$^+$ m/z (%): 494 (M^+ + H, 100), 493 (M^+, 31), 463 (M^+–NO, 41); Anal. Calcd for $C_{24}H_{23}N_5O_5S$: C, 58.41; H, 4.70; N, 14.19. Found: C, 58.57; H, 4.73; N, 14.22.

4.6. Syntheses of 3,4-diphenyl-2-[(3-arylsydnon-4-ylmethylene)hydrazono]-2,3-dihydro-thiazole (7a–d)

To a solution of 2-bromoacetophenone (**4c**, 219 mg, 1.10 mmol) in absolute ethanol (5 mL), were slowly added 3-phenyl-4-formylsydnone 4′-phenylthiosemicarbazone (**3a**, 339 mg, 1.00 mmol) and sodium acetate (246 mg, 3.00 mmol). Acetic acid (0.2 mL) was added to the above solution as a catalyst. The mixed solution was heated at 50 °C for about 10 h until the reaction was completed. The system was then allowed to attain room temperature. The precipitating solid was collected by filtration and washed with ice-cold water and cold ethanol. The collected solid was recrystallized from acetone/ethanol to afford 250 mg (57%) of 3,4-diphenyl-2-[(3-phenylsydnon-4-ylmethylene)hydrazono]-2,3-dihydro-thiazole (**7a**) as orange powder. The chemical and physical spectral characteristics of these products **7a**–**d** are given below.

4.6.1. 3,4-Diphenyl-2-[(3-phenylsydnon-4-ylmethylene)-hydrazono]-2,3-dihydro-thiazole (7a). Orange powder from CH_3COCH_3/EtOH; yield 57%; mp 229–230 °C; IR (KBr) 3052, 1747, 1588, 1512, 1490, 1258 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.62 (s, 1H), 7.05–7.40 (m, 10H), 7.52 (s, 1H), 7.60–7.85 (m, 5H); ^{13}C NMR (DMSO-d_6): δ 102.53, 106.28, 125.67, 128.24, 128.35, 128.47, 128.64, 128.75, 129.06, 130.17, 130.59, 132.34, 134.12, 135.67, 137.32, 139.85, 165.09, 171.19; FABMS$^+$ m/z (%): 440 (M^+ + H, 100), 439 (M^+, 33), 409 (M^+–NO, 46); Anal. Calcd for $C_{24}H_{17}N_5O_2S$: C, 65.59; H, 3.90; N, 15.93. Found: C, 65.52; H, 4.03; N, 15.96.

4.6.2. 3,4-Diphenyl-2-{[3-(4-methylphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole (7b). Orange crystals from CH_3COCH_3/EtOH; yield 48%; mp 241–242 °C; IR (KBr) 3091, 1746, 1583, 1511, 1492, 1260 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.42 (s, 3H), 6.64 (s, 1H), 7.05–7.40 (m, 10H), 7.48 (d, J = 8.4 Hz, 2H), 7.49 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 21.14, 102.61, 106.33, 125.42, 128.27, 128.39, 128.49, 128.67, 128.79, 129.10, 130.58, 130.63, 131.47, 135.94, 137.38, 139.87, 142.67, 164.90, 171.22; FABMS$^+$ m/z (%): 454 (M^+ + H, 100), 453 (M^+, 29), 423 (M^+–NO, 66); Anal. Calcd for $C_{25}H_{19}N_5O_2S$: C, 66.21; H, 4.22; N, 15.44. Found: C, 66.15; H, 4.30; N, 15.43.

4.6.3. 3,4-Diphenyl-2-{[3-(4-methoxyphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole (7c). Orange-red crystal from CH_3COCH_3/EtOH; yield 51%; mp 222–223 °C; IR (KBr) 3062, 1746, 1590, 1510, 1491, 1259 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.86 (s, 3H), 6.66 (s, 1H), 7.01–7.46 (m, 12H), 7.51 (s, 1H), 7.72 (d, J = 8.9 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 56.00, 102.56, 106.36, 115.25, 126.46, 127.18, 128.24, 128.38, 128.47, 128.64, 128.78, 129.08, 130.62, 136.11, 137.38, 139.84, 161.92, 164.89, 171.10; FABMS$^+$ m/z (%): 470 (M^+ + H, 100), 469 (M^+, 37), 439 (M^+–NO, 68); Anal. Calcd for $C_{25}H_{19}N_5O_3S$: C, 63.95; H, 4.08; N, 14.92. Found: C, 63.75; H, 4.16; N, 14.82. X-ray analytical data are listed in Table 1. Further details have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 216224.

4.6.4. 3,4-Diphenyl-2-{[3-(4-ethoxyphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole (7d). Red crystal from CH_3COCH_3/EtOH; yield 48%; mp 203–204 °C; IR (KBr) 3063, 1752, 1590, 1512, 1491, 1260 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.35 (t, J = 7.0 Hz, 3H), 4.12 (q, J = 7.0 Hz, 2H), 6.64 (s, 1H), 7.05–7.45 (m, 12H), 7.51 (s, 1H), 7.69 (d, J = 8.9 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 14.64, 64.04, 102.55, 106.35, 115.60, 126.28, 127.17, 128.24, 128.37, 128.47, 128.63, 128.77, 129.08, 130.62, 136.12, 137.37, 139.84, 161.20, 164.89, 171.08; FABMS$^+$ m/z (%): 484 (M^+ + H, 100), 483 (M^+, 35), 453 (M^+–NO, 50); Anal. Calcd for $C_{26}H_{21}N_5O_3S$: C, 64.58; H, 4.38; N, 14.48. Found: C, 64.42; H, 4.41; N, 14.43.

4.7. Syntheses of 2-[(3-arylsydnon-4-ylmethylene)hydrazono]thiazolidin-4-ones (5e–h)

To a solution of ethyl chloroacetate (**4a**, 184 mg, 1.50 mmol) in absolute ethanol (5 mL), 3-phenyl-4-formylsydnone thiosemicarbazone (**3e**, 263 mg, 1.00 mmol) and sodium acetate (246 mg, 3.00 mmol) were slowly added. Acetic acid (150 μL) was added to the above solution as a catalyst. The mixed solution was heated at 80 °C for about 35 h until the reaction was completed.

The system was allowed to attain room temperature. The precipitating solid was collected by filtration and washed with ice-cold water and cold ethanol. The collected solid was recrystallized from acetone/ethanol to afford 240 mg (79%) of 2-[(3-phenyl-sydnon-4-ylmethylene)hydrazono]thiazolidin-4-one **5e** as yellow needles. The chemical and physical spectral characteristics of these products **5e**–**h** are given below.

4.7.1. 2-[(3-Phenylsydnon-4-ylmethylene)hydrazono]-thiazolidin-4-one (5e). Yellow needles from CH_3COCH_3/EtOH; yield 79%; mp 215–217 °C; IR (KBr) 2995, 2956, 2774, 1785, 1727, 1628, 1249 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.76 (s, 2H), 7.55–7.86 (m, 6H), 11.88 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 33.24, 105.33, 125.69, 130.12, 132.50, 134.10, 141.24, 165.29, 166.26, 174.12; FABMS$^+$ *m/z* (%): 304 (M^+ + H, 100), 303 (M^+, 18), 273 (M^+–NO, 26), 245 (M^+–NO–CO, 18); Anal. Calcd for $C_{12}H_9N_5O_3S$: C, 47.52; H, 2.99; N, 23.09. Found: C, 47.70; H, 3.08; N, 22.90.

4.7.2. 2-{[3-(4-Methylphenyl)sydnon-4-ylmethylene]hydrazono}thiazolidin-4-one (5f). Yellow needles from CH_3COCH_3/EtOH; yield 72%; mp 226–227 °C; IR (KBr) 2996, 2947, 2776, 1782, 1729, 1627, 1251 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H), 3.82 (s, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.81 (s, 1H), 11.92 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 21.14, 33.29, 105.29, 125.41, 130.46, 131.47, 141.41, 142.75, 165.06, 166.24, 174.21; FABMS$^+$ *m/z* (%): 318 (M^+ + H, 100), 317 (M^+, 20), 287 (M^+–NO, 33), 259 (M^+–NO–CO, 52); Anal. Calcd for $C_{13}H_{11}N_5O_3S$: C, 49.21; H, 3.49; N, 22.07; S, 10.10. Found: C, 49.13; H, 3.54; N, 22.08; S, 10.09.

4.7.3. 2-{[3-(4-Methoxyphenyl)sydnon-4-ylmethylene]hydrazono}thiazolidin-4-one (5g). Yellow needles from CH_3COCH_3/EtOH; yield 67%; mp 216–217 °C; IR (KBr) 2988, 2945, 2767, 1783, 1723, 1626, 1252 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.80 (s, 2H), 3.84 (s, 3H), 7.19 (d, J = 9.0 Hz, 2H), 7.72 (d, J = 9.0 Hz, 2H), 7.79 (s, 1H), 11.89 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 33.29, 56.05, 105.33, 115.18, 126.48, 127.21, 141.58, 162.03, 165.09, 166.17, 174.27; FABMS$^+$ *m/z* (%): 334 (M^+ + H, 100), 333 (M^+, 19), 303 (M^+–NO, 20), 275 (M^+–NO–CO, 25); Anal. Calcd for $C_{13}H_{11}N_5O_4S$: C, 46.84; H, 3.33; N, 21.01. Found: C, 46.69; H, 3.46; N, 20.91.

4.7.4. 2-{[3-(4-Ethoxyphenyl)sydnon-4-ylmethylene]hydrazono}thiazolidin-4-one (5h). Yellow needles from CH_3COCH_3/EtOH; yield 82%; mp 223–224 °C; IR (KBr) 2986, 2946, 2770, 1780, 1724, 1630, 1251 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.34 (t, J = 7.0 Hz, 3H), 3.80 (s, 2H), 4.12 (q, J = 7.0 Hz, 2H), 7.17 (d, J = 8.9 Hz, 2H), 7.70 (d, J = 8.9 Hz, 2H), 7.79 (s, 1H), 11.90 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.64, 33.29, 64.10, 105.32, 115.56, 126.31, 127.21, 141.62, 161.33, 165.11, 166.29, 174.27; FABMS$^+$ *m/z* (%): 348 (M^+ + H, 100), 347 (M^+, 18), 317 (M^+–NO, 24); Anal. Calcd for $C_{14}H_{13}N_5O_4S$: C, 48.41; H, 3.77; N, 20.16. Found: C, 48.20; H, 3.88; N, 19.94.

4.8. Syntheses of 4-methyl-2-[(3-arylsydnon-4-ylmethylene)hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6e–h)

To a solution of ethyl 2-chloroacetoacetate (**4b**, 247 mg, 1.50 mmol) in absolute ethanol (5 mL), 3-phenyl-4-formylsydnone thiosemicarbazone (**3e**, 263 mg, 1.00 mmol) and sodium acetate (246 mg, 3.00 mmol) were slowly added. Acetic acid (200 μL) was added to the above solution as a catalyst. The mixed solution was heated at 80 °C for about 24 h until the reaction was completed. The system was then allowed to attain room temperature. The precipitating solid was collected by filtration and washed with ice-cold water and cold ethanol. The collected solid was recrystallized from dichloromethane/ethanol to afford 254 mg (68%) of 4-methyl-2-[(3-phenylsydnon-4-ylmethylene)hydrazono]-2,3-dihydrothiazole-5-carboxylic acid ethyl ester (**6e**) as yellow powder. The chemical and physical spectral characteristics of these products **6e**–**h** are given below.

4.8.1. 4-Methyl-2-[(3-phenylsydnon-4-ylmethylene)-hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6e). Yellow powder from CH_2Cl_2/EtOH; yield 68%; mp 197–198 °C; IR (KBr) 3194, 3074, 2982, 2931, 1760, 1673, 1555, 1272 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.27 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 4.16 (q, J = 7.2 Hz, 2H), 7.57–7.83 (m, 6H), 12.30 (s, 1H); FABMS$^+$ *m/z* (%): 374 (M^+ + H, 100), 373 (M^+, 31), 343 (M^+–NO, 28); Anal. Calcd for $C_{16}H_{15}N_5O_4S$: C, 51.47; H, 4.05; N, 18.76; S, 8.60. Found: C, 51.28; H, 4.19; N, 18.56; S, 8.47.

4.8.2. 4-Methyl-2-{[3-(4-methylphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6f). Yellow powder from CH_2Cl_2/EtOH; yield 55%; mp 186–188 °C; IR (KBr) 3171, 3049, 2984, 2927, 1759, 1704, 1580, 1267 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.25 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 2.45 (s, 3H), 4.17 (q, J = 7.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.63–7.67 (m, 3H), 12.29 (s, 1H); FABMS$^+$ *m/z* (%): 388 (M^+ + H, 100), 387 (M^+, 25), 357 (M^+–NO, 31); Anal. Calcd for $C_{17}H_{17}N_5O_4S$: C, 52.70; H, 4.42; N, 18.08. Found: C, 52.59; H, 4.51; N, 18.07.

4.8.3. 4-Methyl-2-{[3-(4-methoxyphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6g). Yellow needles from CH_2Cl_2/EtOH; yield 62%; mp 191–192 °C; IR (KBr) 3160, 2930, 2908, 2841, 2821, 1756, 1701, 1578, 1256 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.24 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 3.86 (s, 3H), 4.16 (q, J = 7.2 Hz, 2H), 7.21 (d, J = 9.1 Hz, 2H), 7.65 (s, 1H), 7.71 (d, J = 9.1 Hz, 2H), 12.28 (s, 1H); FABMS$^+$ *m/z* (%): 404 (M^+ + H, 100), 403 (M^+, 28), 373 (M^+–NO, 32); Anal. Calcd for $C_{17}H_{17}N_5O_5S$: C, 50.61; H, 4.25; N, 17.36. Found: C, 50.60; H, 4.33; N, 17.31.

4.8.4. 4-Methyl-2-{[3-(4-ethoxyphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester (6h). Yellow needles from CH_2Cl_2/EtOH; yield 73%; mp 194–195 °C; IR (KBr) 3148, 2982, 2905, 1768, 1715, 1266 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.24

(t, $J=7.2$ Hz, 3H), 1.36 (t, $J=6.9$ Hz, 3H), 2.39 (s, 3H), 4.13 (q, $J=6.9$ Hz, 2H), 4.16 (q, $J=7.2$ Hz, 2H), 7.19 (d, $J=9.0$ Hz, 2H), 7.65 (s, 1H), 7.70 (d, $J=9.0$ Hz, 2H), 12.29 (s, 1H); FABMS$^+$ *m/z* (%): 418 ($M^+ + H$, 100), 417 (M^+, 26), 387 (M^+–NO, 35); Anal. Calcd for $C_{18}H_{19}N_5O_5S$: C, 51.79; H, 4.59; N, 16.78. Found: C, 51.62; H, 4.60; N, 16.70.

4.9. Syntheses of 4-phenyl-2-[(3-arylsydnon-4-ylmethylene)hydrazono]-2,3-dihydro-thiazoles (7e–h)

To an ice cooled solution of 3-phenyl-4-formylsydnone thiosemicarbazone (**3e**, 263 mg, 1.00 mmol) in absolute ethanol (5 mL), sodium acetate (246 mg, 3.00 mmol) was slowly added. Acetic acid (150 μL) was added as a catalyst. 2-Bromoacetophenone (**4c**, 209 mg, 1.05 mmol) was slowly added to the above solution over 30 min. The mixed solution was stirred at 0 °C for about 15 h until the reaction was completed. The precipitating solid was collected by filtration and washed with ice-cold water and cold ethanol. The collected solid was recrystallized from acetone/ethanol to yield 247 mg (68%) of 4-phenyl-2-[(3-phenylsydnon-4-ylmethylene)hydrazono]-2,3-dihydro-thiazole (**7e**) as yellow powder. The chemical and physical spectral characteristics of these products **7e**–**h** are given below.

4.9.1. 4-Phenyl-2-[(3-phenylsydnon-4-ylmethylene)hydrazono]-2,3-dihydro-thiazole (7e). Yellow powder from CH_3COCH_3/EtOH; yield 68%; mp 165–166 °C; IR (KBr) 3210, 1728, 1566, 1422, 1265 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.23–7.40 (m, 4H), 7.67–7.84 (m, 8H), 12.17 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 104.35, 105.89, 125.64, 125.69, 126.71, 127.74, 128.75, 130.18, 132.39, 134.19, 134.61, 150.58, 165.29, 167.47; FABMS$^+$ *m/z* (%): 364 ($M^+ + H$, 100), 363 (M^+, 28), 333 (M^+–NO, 29); Anal. Calcd for $C_{18}H_{13}N_5O_2S$: C, 59.49; H, 3.61; N, 19.27; S, 8.80. Found: C, 59.60; H, 3.68; N, 19.33; S, 8.87.

4.9.2. 4-Phenyl-2-{[3-(4-methylphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole (7f). Yellow powder from CH_3COCH_3/EtOH; yield 65%; mp 167–168 °C; IR (KBr) 3212, 1729, 1562, 1423, 1261 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.46 (s, 3H), 7.27 (s, 1H), 7.30–7.45 (m, 3H), 7.52 (d, $J=8.4$ Hz, 2H), 7.65 (s, 1H), 7.69 (d, $J=8.4$ Hz, 2H), 7.72–7.80 (m, 2H), 12.13 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 21.15, 104.43, 105.89, 125.44, 125.64, 126.87, 127.73, 128.77, 130.55, 131.63, 134.65, 142.61, 150.58, 165.11, 167.50; FABMS$^+$ *m/m*z (%): 378 ($M^+ + H$, 100), 377 (M^+, 31), 347 (M^+–NO, 31); Anal. Calcd for $C_{19}H_{15}N_5O_2S$: C, 60.47; H, 4.01; N, 18.56; S, 8.50. Found: C, 60.46; H, 4.07; N, 18.58; S, 8.53.

4.9.3. 4-Phenyl-2-{[3-(4-methoxyphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole (7g). Orange crystals from CH_2Cl_2/EtOH; yield 80%; mp 160–162 °C; IR (KBr) 3189, 1752, 1572, 1250 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.88 (s, 3H), 7.24 (d, $J=8.9$ Hz, 2H), 7.27–7.47 (m, 4H), 7.66 (s, 1H), 7.71–7.82 (m, 4H), 12.14 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 56.06, 104.34, 105.87, 115.22, 125.62, 126.66, 127.01, 127.17, 127.70, 128.72, 134.63, 150.55, 161.94, 165.14, 167.47; FABMS$^+$ *m/z* (%): 394 ($M^+ + H$, 100), 393 (M^+, 19), 363 (M^+–NO, 34); Anal. Calcd for $C_{19}H_{15}N_5O_3S$: C, 58.01; H, 3.84; N, 17.80; S, 8.15. Found: C, 57.87; H, 3.90; N, 17.65; S, 8.16.

4.9.4. 4-Phenyl-2-{[3-(4-ethoxyphenyl)sydnon-4-ylmethylene]hydrazono}-2,3-dihydro-thiazole (7h). Yellow powder from CH_3COCH_3/EtOH; yield 68%; mp 164–165 °C; IR (KBr) 3192, 1721, 1556, 1244 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.38 (t, $J=7.0$ Hz, 3H), 4.16 (q, $J=7.0$ Hz, 2H), 7.21 (d, $J=9.0$ Hz, 2H), 7.27 (s, 1H), 7.29–7.50 (m, 3H), 7.65 (s, 1H), 7.72 (d, $J=9.0$ Hz, 2H), 7.76–7.90 (m, 2H), 12.13 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.65, 64.11, 104.33, 105.88, 115.63, 125.65, 126.50, 127.04, 127.19, 127.73, 128.75, 134.64, 150.61, 161.23, 165.17, 167.50; FABMS$^+$ *m/z* (%): 408 ($M^+ + H$, 100), 407 (M^+, 22), 377 (M^+–NO, 31); Anal. Calcd for $C_{20}H_{17}N_5O_3S$: C, 58.96; H, 4.21; N, 17.19; S, 7.90. Found: C, 59.00; H, 4.28; N, 17.20; S, 7.95.

4.10. Scavenging effect on 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical[35–37]

The scavenging effect of the synthesized compounds **5a**–**7h** on the DPPH radical was evaluated according to the methods of Shimada et al.,[35] Leong and Shui[36] and Braca et al.[37] Various concentrations of the test compound in 1.5 mL methanol were added to a 1.5 mL (0.2 mM) solution of DPPH radical in methanol (final concentration of DPPH was 0.1 mM). The mixture was shaken vigorously and allowed to stand for 30 min; absorbance at 517 nm was determined (Hitachi U-2001 spectrophotometer), and the percentage of activity was calculated. Vitamin E was used as a reference compound. All tests and analyses were undertaken on three replicates and the results averaged.

Scavenging activity (%) = $\{[(Ab + As) - Am]/Ab\} \times 100\%$; Ab: absorbance of 0.1 mM DPPH methanol solution at 517 nm; As: absorbance of various concentration solution of test compound at 517 nm; Am: absorbance of mixture methanol solution at 517 nm.

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