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An efficient and green procedure for synthesis of rhodanine derivatives by aldol-thia-Michael protocol using aqueous diethylamine medium†

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A simple, economical, and green approach to the synthesis of rhodanine derivatives using a tandem aldol condensation-thia-Michael addition process in aqueous diethylamine medium was described. The experiment protocol features simple operations, and the products were isolated in high to excellent yields (82–96%). As spontaneous precipitation always occurs at the end of the process, this leads to easy separation of the products *via* a simple filtration.

Introduction

The five-membered rhodanine core is an interesting heterocyclic ring system featured in a large number of natural or synthetic compounds with a wide range of pharmacological activities.[1] Rhodanine derivatives have been reported as small molecule inhibitors for targets such as hepatitis C virus NS5B polymerase[2] and human cathepsin D.[3] Furthermore, they have been reported as antimalarial, antiviral, antibacterial, and anticancer, and antidiabetic agents (Fig. 1).[4] Epalrestat is a well-known and highly marketed drug comprising the rhodanine nuclei and used to delay the progression of diabetic neuropathy.

It is therefore not surprising that numerous synthetic routes have been developed to obtain this heterocyclic core, many of which were recently reported.[6] Due to stringent and growing environmental regulations, organic chemists have endeavored to develop clean, economical, and environmentally safer methodologies.[7] Current emphasis on the development of multiple chemical transformations sequentially performed in a single reaction vessel, without intermediary purification steps, has led to the generation of a variety of molecular complexity. The benefits of the green approach are based on reduced time, costs, and waste generation, but compatibility and reliability must be circumvented for such processes to become attractive for industrial purposes. During the past decade, aldol-thia-Michael protocol is an important process in organic chemistry and has versatile applications in organic synthesis.[8] Different catalysts and reaction media have been employed, such as Lewis acids, cinchona alkaloids, ionic liquids, and solid support.[9] One of the most promising approaches is using water as the reaction medium as reported by Saeed Abaee, M. *et al.* on a multicomponent synthesis of β-aryl-β-mercapto ketones.[10]

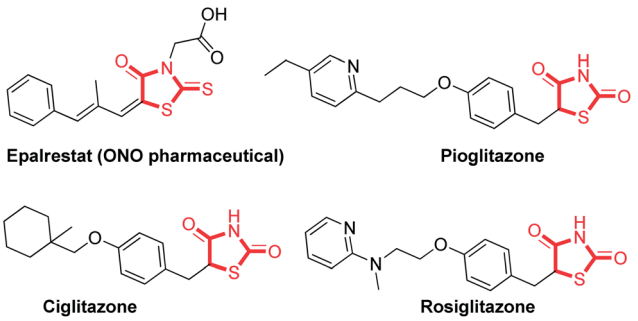

Fig. 1 Bioactive compounds containing the rhodanine and thiazolidinedione framework.[5]

With this in mind and in continuation of our research program on the developments of new routes to heterocyclic system,[11] we now report the aldol-thia-Michael addition process for the synthesis of rhodanine derivatives where water is used as a green solvent in the presence of diethylamine. These products were subjected for biological and pharmacological evaluation.

Results and discussion

In a preliminary experiment, treatment of 2-thioxothiazolidin-4-one (**1**) with benzaldehyde (**2**) using water–diethylamine at room temperature for 3 h (TLC control) afforded the (*Z*)-5-benzylidene-2-thioxothiazolidin-4-one adduct (**3a**·**HNEt$_2$**).[12] The

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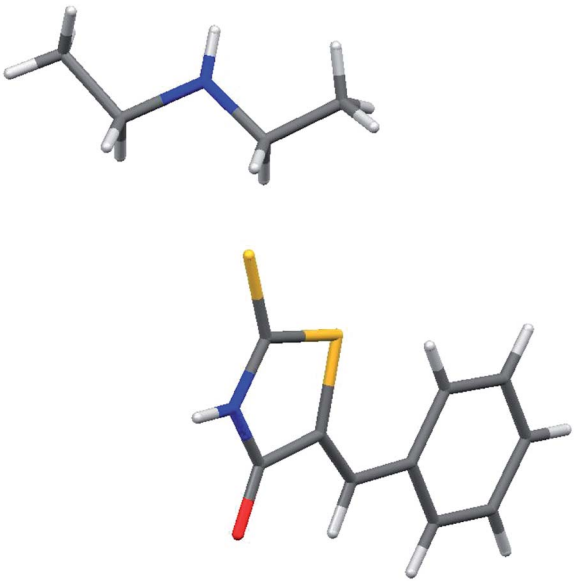


Fig. 2 X-ray diffraction structure of compound **3a·HNEt$_2$**.

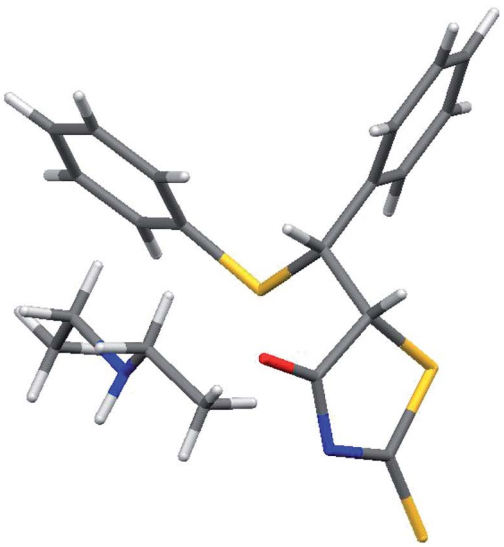


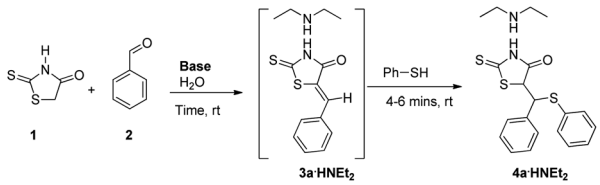
Fig. 3 X-ray diffraction structure of compound **4a·HNEt$_2$**.

configuration of its double bond was determined on the basis of X-ray diffraction analysis of its salt with diethylamine (Fig. 2). Subsequently, addition of thiophenol to the mixture at this point led to quantitative consumption of the reactants within a few minutes and the formation of **4a·HNEt$_2$** in 96% yield (entry 1). The structures of products **3a·HNEt$_2$** and **4a·HNEt$_2$** were identified by their spectroscopy analysis. The structure of **4a·HNEt$_2$** was further confirmed by X-ray diffraction analysis. The molecular structure of **4a·HNEt$_2$** is shown in Fig. 3. Interestingly, the X-ray shown that **4a·HNEt$_2$** has been formed with a molecule of diethylamine as a salt (Fig. 3). Encouraged by this result, we proceeded to study the effect of different amines and reaction conditions on the aldol-thia-Michael addition process for the synthesis of rhodanines derivatives.

Table 1 Screening of conditions for the aldol-thia-Michael addition reaction of model substrate[a]

Entry	Condition	Time [h]	Yield[b] (%)
1	Et_2NH–H_2O	3	96
2	$^iPr_2NH$–H_2O	4	89
3	$(Cyclohexyl)_2NH$–H_2O	4	83
4	Morpholine–H_2O	3	80
5	NaOH–H_2O	6	70
6	Et_2NH	10	10
7	H_2O	10	0

[a] All reactions were carried out with 2-thioxothiazolidin-4-one **1** (3.0 mmol), benzaldehyde **2** (3.0 mmol) and diethylamine (3.0 mmol) in water (2–3 ml) for the specified time for aldol condensation. [b] Yield of isolated product **4a·HNEt$_2$**.



Scheme 1 Model substrate during the optimization studies.

As shown in Table 1, it was found that iPr_2NH–H_2O afford the aldol-thia-Michael adduct in excellent yield 89% (Table 1, entry 2). Other secondary amines, such as $(cyclohexyl)_2NH$ and morpholine, behaved similarly and generated the respective products (Table 1, entry 3 and 4) but showed lower efficiencies as evidenced by the 83% and 80% yield respectively. NaOH was also tested, and was found to be less efficient in the reaction; only moderate yield was obtained (Table 1, entries 5). The products could not be obtained in the absence of either amine (entry 6) or water (entry 7), *i.e.* the reaction either could not be processed or preceded too slowly to be detected. Collectively, the best result with respect to yield was obtained by performing the reaction by the combined promoting effects of both water and diethylamine (Scheme 1).

A plausible mechanism can be proposed for the reaction as shown in Fig. 4. First, the hydrogen bonding activation of the C=O group by water eases up the deprotonation of **1** by

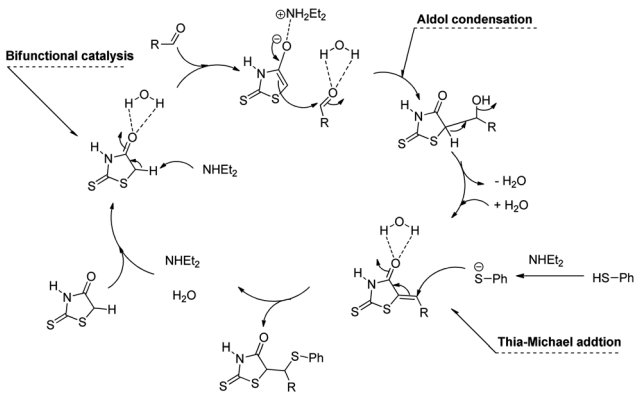


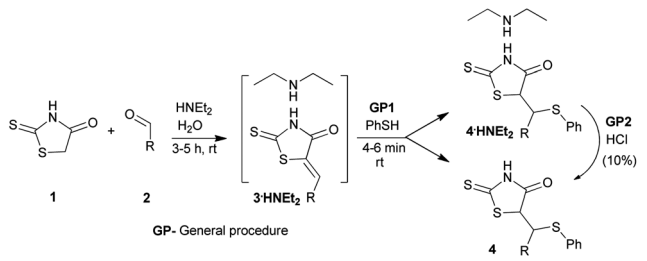
Fig. 4 A possible mechanistic pathway.

diethylamine. The aldehyde is then attacked by the enolate to form the aldol condensation product after dehydration of the intermediate. The second thia-Michael addition under these conditions produces the final product **4** (Fig. 4).[13]

To support the proposed mechanism, the reaction was stopped before the addition of the thiophenol and after TLC showed complete consumption of aldehyde and 2-thioxothiazolidin-4-one. Analysis of the reaction mixture showed the presence of the single product **3·HNEt$_2$** in quantitative yield. Furthermore, the intermediate products **3b,c·HNEt$_2$** were separated and confirmed by X-ray crystal structure determination (see ESI).†

In continuation of our on going program aimed at the synthesis of rhodanine derivatives, the substrate scope was then investigated. We applied the conditions to reactions of **1** with a variety of other aldehydes followed by addition thiophenol. As revealed in Table 2, (entry 1–18). The reactions proved to work well with a range of aldehydes bearing either electron-withdrawing or electron-donating groups to give the rhodanine derivatives **4** with very good to excellent yields (82–96%). Depending on the structure of the reacting aldehyde the products were isolated as adduct with diethylamine (Table 2, entries

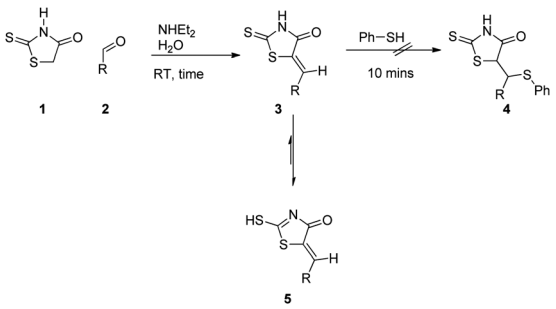
Table 2 The synthesis of aldol-thia-Michael product in diethylamine–water medium[a]



Entry	Product	R	Yield (%)
1	**4a·HNEt2**	Ph	96[b]
2	**4a**	Ph	93[c]
3	**4b**	*p*-CH_3Ph	95[c]
4	**4c·HNEt$_2$**	*p*-ClPh	92[b]
5	**4c**	*p*-ClPh	91[c]
6	**4d·HNEt$_2$**	*p*-BrPh	90[b]
7	**4d**	*p*-BrPh	90[c]
8	**4e**	*p*-CH_3OPh	88[c]
9	**4f**	2,4,6-$(CH_3)_3$Ph	83[c]
10	**4g·HNEt$_2$**	*p*-NO_2Ph	85[b]
11	**4g**	*p*-NO_2Ph	85[c]
12	**4h·HNEt$_2$**	Naphthyl	91[b]
13	**4h**	Naphthyl	90[c]
14	**4i·HNEt$_2$**	2,4-Cl_2Ph	82[b]
15	**4i**	2,4-Cl_2Ph	81[c]
16	**4j**	2,6-Cl_2Ph	80[c]
17	**4k·HNEt$_2$**	*m*-CH_3Ph	89[b]
18	**4k**	*m*-CH_3Ph	87[c]

[a] All reactions were carried out with 2-thioxothiazolidin-4-one **1** (3.0 mmol), aldehyde **2** (3.0 mmol) and diethylamine (3.0 mmol) in water (2–3 ml) for the specified time. [b] Yield of the product isolated directly from the reaction mixture (GP1). [c] Yield of isolated product **4** obtained by treatment of the corresponding salt **4·HNEt$_2$** with aqueous HCl (10%) followed by extraction with DCM/EtOH (GP2).

Table 3 The synthesis of aldol condensed product in diethylamine/water medium[a]



Entry	3	R	Yield[b] (%)
1	**3d**		93
2	**3e**		91
3	**3f**		95
4	**3g**		90

[a] All reactions were carried out with 2-thioxothiazolidin-4-one **1** (3.0 mmol), aldehyde **2** (3.0 mmol) and diethylamine (3.0 mmol) in water (2–3 ml) for the specified time. [b] Yield of isolated product **3d–f**.

1, 4, 6, 10, 12, 14, and 17) or as individual compounds (entries 2, 3, 5, 7–9, 11, 13, 15, 16 and 18). In the case of adducts **4·HNEt$_2$**, the corresponding free rhodanine derivatives **4** can be obtained by treatment with 10% aqueous HCl.

Interesting and surprising was the fact that a variety of heterocyclic aldehydes reacted under the optimized conditions to always yield exclusively the product **3**. A possible explanation of such behaviour is that the heterocyclic fragment is probably more conjugated with the double bond because of less steric factor due to smaller cycles (Table 3, entry 1–3) and/or absence of one *ortho*-proton (Table 3, entry 4). As summarized in Table 3, various heterocyclic aldehyde such as thiophene-2-carbaldehyde, furan-2-carbaldehyde, 1*H*-pyrrole-2-carbaldehyde and picolinaldehyde were reacted with 2-thioxothiazolidin-4-one using diethylamine–water medium afforded mainly product **5** in excellent yield (91–95%). It has been observed that when furan-2-carbaldehyde was used, the product was a mixture of **3** and **5** (Table 3, entry 2). ^{1}HNMR spectrum shown a characteristic broad singlet at δ 13.67 ppm and δ 8.1 ppm which is assigned to the proton of thiol tautomer **5** and the proton of NH tautomer **3** respectively.

Conclusions

In summary, a general and efficient procedure has been developed for facile synthesis of rhodanine derivatives. Reactions occur under mild aqueous conditions using quantities of

diethylamine. More importantly, the products precipitate spontaneously in the mixture allowing their convenient purification without costly and time consuming chromatographic separations. The reactions gave high yields of products in short times. The full scope, asymmetric transformations and its applications in the synthesis of biologically active molecules are currently underway in our laboratory.

Experimental section

General: All the chemicals were purchased from Aldrich, Sigma-Aldrich, Fluka *etc.*, and were used without further purification, unless otherwise stated. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer. ^{1}H-NMR (400 MHz), and ^{13}C-NMR (100 MHz) were run in either deuterated dimethylsulphoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$). Chemical shifts (δ) are referred in terms of ppm and *J*-coupling constants are given in Hz. Mass spectra were recorded on a Jeol of JMS-600H. Elemental analysis was carried out on Elmer 2400 Elemental Analyzer; CHN mode.

General procedure for aldol condensation thia-Michael addition for the synthesis of 4·HNEt$_2$ (GP1)

A mixture of aldehyde **2** (3 mmol, 318 mg), 2-thioxothiazolidin-4-one **1** (3 mmol, 400 mg), and diethylamine (3 mmol, 310 μl) in 3 ml of degassed H_2O was stirred at room temperature for 3–5 hours until TLC showed complete disappearance of the reactants. The thiol (3 mmol, 330 mg) was added to this mixture and stirring was continued for another 4–6 min until TLC showed completion of the reaction. The product precipitated and the mixture was filtered and the solid portion was recrystallized from a mixture of DCM/EtOH to obtain the pure product **4·HNEt$_2$**.

General procedure for aldol condensation thia-Michael addition for the synthesis of 4 (GP2)

A mixture of aldehyde **2** (3 mmol, 318 mg), 2-thioxothiazolidin-4-one **1** (3 mmol, 400 mg), and diethylamine (3 mmol, 310 μl) in 3 ml of degassed H_2O was stirred at room temperature for 3–5 hours until TLC showed complete disappearance of the reactants. The thiol (3 mmol, 330 mg) was added to this mixture and stirring was continued for another 4–6 min until TLC showed completion of the reaction. Water (3 ml) was the added into the reaction mixture, then extracted with DCM/EtOH (3 × 50 ml) and the organic phase washed with 10% HCl (2 × 50 ml), followed by brine (2 × 50 ml), and dried over $MgSO_4$, and filtered and evaporated to afford **4**.

5-(Phenyl(phenylthio)methyl)-2-thioxothiazolidin-4-one compound with diethylamine (1 : 1) (4a·HNEt$_2$). **4a·HNEt$_2$** was prepared from 2-thioxothiazolidin-4-one **1**, benzaldehyde and thiophenol according to the general procedure (GP1) yielding yellow crystalline materials (1.17 g, 2.9 mmol, 96%). m.p: 180 °C; IR (KBr, cm^{-1}): 3458, 3035, 2972, 1738, 1363, 1222; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.33 (bs, NH), 7.51–7.22 (m, 11H, CH & CH & 2Ph), 2.94 (q, 4H, J = 7.3 Hz, CH_2CH$_3$), 1.16 (t, 6H, J = 7.3 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 203.2, 182.7, 136.3, 135.5, 135.4, 130.1, 130.0, 129.5, 128.1, 127.7, 124.7, 41.9, 11.6; LC/MS (ESI): 404 [M]$^+$; anal. for $C_{20}H_{24}N_2OS_3$; calcd: C, 59.37; H, 5.98; N, 6.92; found: C, 59.40; H, 6.01; N, 6.90.%

The structure of **4a·HNEt$_2$** was confirmed by X-ray crystal structure analysis. A crystal suitable for X-ray analysis of the compound formed in DCM/EtOH at room temperature gives yellow crystal.†

5-(Phenyl(phenylthio)methyl)-2-thioxothiazolidin-4-one (4a). **4a** was prepared from 2-thioxothiazolidin-4-one **1**, benzaldehyde and thiophenol according to the general procedure (GP2) to yielding yellow materials (0.93 g, 2.79 mmol, 93%). m.p: 179 °C; IR (KBr, cm^{-1}): 3455, 3010, 2965, 1745, 1360, 1225; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.53–7.30 (m, 13H, NH & CH & CH & 2Ph), 2.33 (s, 3H, CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 196.3, 170.0, 133.5, 132.2, 131.3, 131.0, 130.0, 129.7, 129.0, 128.2, 127.8, 126.1, 125.4; LC/MS (ESI): 331 [M]$^+$; anal. for $C_{16}H_{13}NOS_3$; calcd: C, 57.97; H, 3.95; N, 4.23; found: C, 60.00; H, 3.92; N, 4.25.%

5-((Phenylthio)(*p*-tolyl)methyl)-2-thioxothiazolidin-4-one (4b). **4b** was prepared from 2-thioxothiazolidin-4-one **1**, tolualdehyde and thiophenol according to the general procedure (GP2) to yielding yellow needle materials (983 mg, 2.85 mmol, 95%). m.p: 140 °C; IR (KBr, cm^{-1}): 3458, 3016, 2970, 1738, 1365, 1227; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.51–7.33 (m, 11H, CH & CH & 2Ph), 2.33 (s, 3H, CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 196.2, 170.0, 141.7, 136.3, 132.3, 131.0, 130.7, 130.6, 130.0, 128.1, 127.7, 21.6; LC/MS (ESI): 345 [M]$^+$; anal. for $C_{17}H_{15}NOS_3$; calcd: C, 59.10; H, 4.38; N, 4.05; found: C, 59.12; H, 4.40; N, 4.09.%

5-((4-Chlorophenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one compound with diethylamine (1 : 1) (4c·HNEt$_2$). **4c·HNEt$_2$** was prepared from 2-thioxothiazolidin-4-one **1**, *p*-chlorobenzaldehyde and thiophenol according to the general procedure (GP1) yielding yellow powder (1.21 g, 2.76 mmol, 92%). m.p: 103 °C; IR (KBr, cm^{-1}): 3459, 3035, 2973, 1738, 1365, 1226; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.34 (bs, 1H, NH), 7.52 (d, 2H, J = 8.0 Hz, Ph), 7.38 (d, 2H, J = 8.0 Hz, CH & CH), 7.36 (d, 2H, J = 8.0 Hz, Ph), 7.30–7.21 (m, 5H, Ph), 2.94 (q, 2H, J = 6.6 Hz, CH_2CH$_3$), 1.16 (t, 3H, J = 6.6 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 202.6, 182.7, 136.3, 136.1, 134.4, 133.6, 131.7, 130.0, 129.8, 129.6, 128.1, 127.7, 123.4, 41.9, 11.6; LC/MS (ESI): 439 [M]$^+$; anal. for $C_{20}H_{23}ClN_2OS_3$; calcd: C, 54.71; H, 5.28; N, 6.38; found: C, 54.70; H, 5.25; N, 6.37.%

5-((4-Chlorophenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one (4c). **4c** was prepared from 2-thioxothiazolidin-4-one **1**, *p*-chlorobenzaldehyde and thiophenol according to the general procedure (GP2) yielding yellow powder (0.99 g, 2.73 mmol, 91%). m.p: 189 °C; IR (KBr, cm^{-1}): 3445, 3021, 2986, 1710, 1365, 1220; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.68–7.29 (m, 12H, NH & CH & CH & Ph); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 196.0, 170.0, 136.0, 132.6, 132.5, 130.8, 130.1, 129.7, 129.0, 127.8, 126.9, 125.5; LC/MS (ESI): 365 [M]$^+$; anal. for $C_{16}H_{12}ClNOS_3$; calcd: C, 52.52; H, 3.31; Cl, 9.69; N, 3.83; found: C, 52.51; H, 3.32; Cl, 9.71; N, 3.86.%

5-((4-Bromophenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one compound with diethylamine (1 : 1) (4d·HNEt$_2$). **4d·HNEt$_2$** was prepared from 2-thioxothiazolidin-4-one **1**, *p*-bromobenzaldehyde and thiophenol according to the general procedure (GP1) yielding yellow needle (931 mg, 2.7 mmol, 90%). m.p: 240 °C; IR (KBr, cm^{-1}): 3458, 3015, 2970, 1738, 1365, 1227; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.30 (bs, 1H, NH), 7.69 (d, 2H, J = 8.0 Hz, Ph), 7.53 (d, 2H, J = 8.0 Hz, CH & CH), 7.49 (d, 2H, J = 8.0 Hz, Ph), 7.40–7.22 (m, 5H, Ph), 2.92 (q, 2H, J = 6.6 Hz, CH_2CH$_3$), 1.16 (t, 3H, J = 6.6 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 200.2, 167.1, 134.1, 134.1, 132.6, 132.2, 130.0, 128.1, 127.7, 125.9, 123.2, 41.5, 11.6; LC/MS (ESI): 345 [M]$^+$; anal. for $C_{20}H_{23}BrN_2OS_3$; calcd: C, 49.68; H, 4.79; N, 5.79; found: C, 49.70; H, 4.76; N, 5.81.%

5-((4-Bromophenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one (4d). **4d** was prepared from 2-thioxothiazolidin-4-one **1**, *p*-bromobenzaldehyde and thiophenol according to the general procedure (GP2) yielding yellow powder (1.10 g, 2.7 mmol, 90%). m.p: 220 °C; IR (KBr, cm^{-1}): 3455, 3015, 2970, 1735, 1365, 1225; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.85–7.29 (m, 12H, NH & CH & CH & Ph); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 196.0, 170.0, 133.0, 132.8, 131.6, 130.9, 130.0, 129.6, 128.2, 1227.7, 126.9, 124.9; LC/MS (ESI): 408 [M]$^+$; anal. for $C_{16}H_{12}BrNOS_3$; calcd: C, 46.83; H, 2.95; Br, 19.47; N, 3.41; found: C, 46.85; H, 2.94; Br, 19.50; N, 3.40.%

5-((4-Methoxyphenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one (4e). **4e** was prepared from 2-thioxothiazolidin-4-one **1**, *p*-methoxybenzaldehyde and thiophenol according to the general procedure (GP2) yielding yellow powder (953 mg, 2.64 mmol, 88%). m.p: 190 °C; IR (KBr, cm^{-1}): 3458, 3016, 2970, 1738, 1366, 1228; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.60 (bs, 1H, NH), 7.57 (d, 2H, J = 8.8 Hz, Ph), 7.53 (d, 2H, J = 8.0 Hz, CH & CH), 7.44–7.27 (m, 5H, Ph), 7.11 (d, 2H, J = 8.8 Hz, Ph), 3.86 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 196.0, 169.9, 161.9, 136.3, 133.2, 130.0, 128.1, 127.7, 126.0, 122.7, 115.6, 56.1; LC/MS (ESI): 361 [M]$^+$; anal. for $C_{17}H_{15}NO_2S_3$; calcd: C, 56.48; H, 4.18; N, 3.87; found: C, 56.51; H, 4.18; N, 3.88.%

5-(Mesityl(phenylthio)methyl)-2-thioxothiazolidin-4-one (4f). **4f** was prepared from 2-thioxothiazolidin-4-one **1**, mesitylaldehyde and thiophenol according to the general procedure (GP2) to yielding yellow powder (928 mg, 2.49 mmol, 83%). m.p: 180 °C; IR (KBr, cm^{-1}): 3460, 3016, 2970, 1738, 1365, 1227; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.46 (s, 1H, NH), 7.56–7.28 (m, 7H, CH & CH & Ph), 6.97 (s, 1H, Ph), 6.91 (s, 1H, Ph), 2.28 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$) 2.11 (s, 3H, CH$_3$); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 193.9, 143.9, 141.3, 136.3, 135.5, 130.8, 130.0, 128.9, 128.1, 127.7, 21.5, 21.2, 20.5, 20.2; LC/MS (ESI): 373 [M]$^+$; anal. for $C_{19}H_{19}NOS_3$; calcd: C, 61.09; H, 5.13; N, 3.75; found: C, 61.10; H, 5.11; N, 3.78.%

5-((4-Nitrophenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one (4g). **4g** was prepared from 2-thioxothiazolidin-4-one **1**, *p*-nitrobenzaldehyde and thiophenol according to the general procedure (GP2) to yielding powder (1.14 g, 2.55 mmol, 85%). m.p: 170 °C; IR (KBr, cm^{-1}): 3454, 3019, 2970, 1738, 1365, 1222; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 8.26 (d, 1H, J = 8.8 Hz, CH), 7.62 (d, 1H, J = 8.8 Hz, CH), 7.49 (d, 2H, J = 7.3 Hz, Ph), 7.36–7.19 (m, 7H, 2Ph), 3.16 (q, 2H, J = 6.6 Hz, CH_2CH$_3$), 1.37 (t, 3H, J = 6.6 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, CDCl$_3$): 206.9, 183.2, 147.1, 141.1, 137.0, 130.5, 130.5, 129.2, 128.3, 127.5, 127.2, 124.2, 42.7, 11.6; LC/MS (ESI): 449 [M]$^+$; anal. for $C_{20}H_{23}N_3O_3S_3$; calcd: C, 53.43; H, 5.16; N, 9.35; found: C, 53.45; H, 5.15; N, 9.36.%

5-(Naphthalen-1-yl(phenylthio)methyl)-2-thioxothiazolidin-4-one compound with diethylamine (1 : 1) (4h·HNEt$_2$). **4h·HNEt$_2$** was prepared from 2-thioxothiazolidin-4-one **1**,2-naphthaldehyde and thiophenol according to the general procedure (GP1) as yellow powder (1.24 g, 2.73 mmol, 91%). m.p: 160 °C; IR (KBr, cm^{-1}): 3458, 3031, 2970, 1738, 1663, 1348, 1216; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.40 (s, NH), 9.16 (d, 1H, J = 8.0 Hz, naphthyl) 8.27–7.29 (m, 13H, CH, CH, naphthyl, Ph), 2.92 (q, 2H, J = 6.6 Hz, CH_2CH$_3$), 1.16 (t, 3H, J = 6.6 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 198.7, 194.9, 137.3, 136.3, 135.8, 133.8, 132.1, 131.6, 131.4, 131.2, 131.1, 130.3, 130.0, 129.5, 129.4, 129.2, 128.1, 127.9, 127.7, 127.4, 127.2, 126.2, 125.9, 124.6, 123.8, 41.7, 11.6; LC/MS (ESI): 454 [M]$^+$; anal. for $C_{24}H_{26}N_2OS_3$; calcd: C, 63.40; H, 5.76; N, 6.16; found: C, 63.43; H, 5.75; N, 6.15.%

5-(Naphthalen-2-yl(phenylthio)methyl)-2-thioxothiazolidin-4-one (4h). **4h** was prepared from 2-thioxothiazolidin-4-one **1**,2-naphthaldehyde and thiophenol according to the general procedure (GP2) as yellow powder (1.028 g, 2.70 mmol, 90%). m.p: 135 °C; IR (KBr, cm^{-1}): 3435, 3040, 2986, 1735, 1660, 1441, 1350, 1226, 1185; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.46 (s, NH), 9.20 (d, 1H, J = 8.0 Hz, naphthyl) 8.30–7.32 (m, 13H, CH, CH, naphthyl, Ph); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 195.0, 169.4, 137.4, 135.8, 133.9, 131.8, 131.6, 130.7, 130.4, 129.6, 129.5, 129.3, 128.9, 128.7, 128.2, 127.7, 127.5, 126.3, 125.9, 124.7, 123.9, 122.4,; LC/MS (ESI): 381 [M]$^+$; anal. for $C_{20}H_{15}NOS_3$; calcd: C, 62.96; H, 3.96; N, 3.67; found: C, 62.99; H, 3.92; N, 3.65.%

5-((2,4-Dichlorophenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one compound with diethylamine (1 : 1) (4i·HNEt$_2$). **4i·HNEt$_2$** was prepared from 2-thioxothiazolidin-4-one **1**,2,4-dichlorobenazaldehyde and thiophenol according to the general procedure (GP1) yielding yellow powder (1.16 g, 2.46 mmol, 82%). m.p: 85 °C; IR (KBr, cm^{-1}): 3458, 3022, 2970, 1738, 1348, 1216; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.37 (bs, 1H, NH), 7.72 (s, 1H, Ph), 7.61–7.27 (m, 9H, CH & CH & Ph), 2.92 (q, 2H, J = 6.6 Hz, CH_2CH$_3$), 1.16 (t, 3H, J = 6.6 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 202.1, 181.7, 138.8, 136.3, 135.4, 134.1, 132.3, 130.6, 130.0, 129.5, 128.9, 128.6, 128.1, 128.0, 127.7, 118.6, 41.9, 11.5; LC/MS (ESI): 473 [M]$^+$; anal. for $C_{20}H_{22}Cl_2N_2OS_3$; calcd: C, 50.73; H, 4.68; Cl, 14.97; N, 5.92; found: C, 50.72; H, 4.70; Cl, 5.01; N, 5.90.%

5-((2,4-Dichlorophenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one (4i). **4i** was prepared from 2-thioxothiazolidin-4-one **1**,2,4-dichlorobenazaldehyde and thiophenol according to the general procedure (GP2) yielding yellow powder (0.97 g, 2.43 mmol, 81%). m.p: 55 °C; IR (KBr, cm^{-1}): 3445, 3010, 2965, 1722, 1335, 1225, 1175; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.64–7.24 (m, 11H, NH & CH & CH & Ph); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 200.7, 188.9, 141.3, 138.7, 135.5, 133.7, 132.6, 131.7, 130.6, 129.5, 128.9, 128.2, 127.9, 127.5, 125.7; LC/MS (ESI): 399 [M]$^+$; anal. for $C_{18}H_{11}Cl_2NOS_3$; calcd: C, 48.00; H, 2.77; Cl, 17.71; N, 3.50; found: C, 48.03; H, 2.78; Cl, 17.67; N, 3.48.%

5-((2,6-Dichlorophenyl)(phenylthio)methyl)-2-thioxothiazolidin-4-one (4j). 4j was prepared from 2-thioxothiazolidin-4-one **1**,2,6-dichlorobenazaldehyde and thiophenol according to the general procedure (GP2) to yielding yellow powder (960 mg, 2.4 mmol, 80%). m.p: 165 °C; IR (KBr, cm^{-1}): 3458, 3022, 2970, 1738, 1348, 1216; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.36 (bs, 1H, NH), 7.64–7.27 (m, 10H, CH & CH & Ph); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 194.3, 168.5, 134.5, 134.19, 131.5, 131.1, 130.7, 129.1, 129.0, 128.6, 128.3, 128.0, 127.9, 127.5, 127.2; LC/MS (ESI): 400 $[M]^+$; anal. for $C_{16}H_{11}Cl_2NOS_3$; calcd: C, 48.00; H, 2.77; N, 3.50; found: C, 48.05; H, 2.76; N, 3.51.%

5-((Phenylthio)(*m*-tolyl)methyl)-2-thioxothiazolidin-4-one compound with diethylamine (1 : 1) (4k·HNEt$_2$). 4k·HNEt$_2$ was prepared from 2-thioxothiazolidin-4-one **1**,3-methylbenzaldehyde and thiophenol according to the general procedure (GP1) yielding yellow powder (1.11 g, 2.67 mmol, 89%). m.p: 145 °C; IR (KBr, cm^{-1}): 3458, 3035, 2972, 1738, 1363, 1222; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.30 (bs, NH), 7.49 (d, 2H, J = 7.3 Hz, Ph),7.39 (s, 1H, Ph),7.31–7.11 (m, 8H, CH & CH & Ph), 3.14 (q, 4H, J = 7.3 Hz, CH_2CH$_3$),2.31 (s, 3H, CH$_3$), 1.36 (t, 6H, J = 7.3 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.0, 182.6, 138.8, 134.5, 132.7, 130.9, 130.5, 129.4, 129.1, 129.0, 128.7, 127.6, 127.2, 125.6, 42.8, 21.5, 11.6; LC/MS (ESI): 418 $[M]^+$; anal. for $C_{21}H_{26}N_2OS_3$; calcd: C, 60.25; H, 6.26; N, 6.69; found: C, 60.22; H, 6.25; N, 6.70.%

5-((Phenylthio)(*m*-tolyl)methyl)-2-thioxothiazolidin-4-one)) (4k). 4k was prepared from 2-thioxothiazolidin-4-one **1**,3-methylbenzaldehyde and thiophenol according to the general procedure (GP2) yielding yellow powder (0.90 g, 2.61 mmol, 87%). m.p: 171 °C; IR (KBr, cm^{-1}): 3446, 3009, 2960, 1698, 1445, 1225; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57–7.32 (m, 10H, NH & CH & CH & Ph), 2.37 (s, 3H, CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.3, 169.9, 139.4, 133.5, 132.3, 132.0, 131.5, 130.0, 129.9, 128.2, 128.1, 127.7, 125.8, 21.5; LC/MS (ESI): 345 $[M]^+$; anal. for $C_{17}H_{15}NOS_3$; calcd: C, 59.10; H, 4.38; N, 4.05; found: C, 59.13; H, 4.41; N, 4.07.%

General procedure for the synthesis of 3·HNEt$_2$ (GP3)

A mixture of aldehyde **2** (3 mmol, 318 mg), 2-thioxothiazolidin-4-one **1** (3 mmol, 400 mg), and Et_2NH (3 mmol, 310 μl) in 3 ml of degassed H_2O was stirred at room temperature for 3–5 hours until TLC showed complete disappearance of the reactants. The product precipitated and the mixture was filtered and the solid portion was recrystallized to obtain the pure product **3·HNEt$_2$.**

(*Z*)-5-Benzylidene-2-thioxothiazolidin-4-one compound with diethylamine (1 : 1) (3a·HNEt$_2$). 3a·HNEt$_2$ was prepared from 2-thioxothiazolidin-4-one **1**, and benzaldehyde according to general procedure (GP3) as yellow crystalline materials; IR (KBr, cm^{-1}): 3458, 3016, 2970, 1738, 1430, 1366, 1228; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.38 (bs, 1H, NH), 7.55–7.47 (m, 5H, Ph), 7.41 (s, 1H, CH), 2.95 (q, 4H, J = 13.9 Hz, CH_2CH$_3$), 1.16 (t, 6H, J = 7.3 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 200.1, 177.3, 134.6, 130.5, 130.1, 129.7, 128.0, 41.9, 11.6; LC/MS (ESI): 294 $[M]^+$; anal. for $C_{14}H_{18}N_2OS_2$; calcd: C, 57.11; H, 6.16; N, 9.51; found: C, 57.12; H, 6.16; N, 9.50.%

The structure **3a·HNEt$_2$** was confirmed by X-ray crystal structure analysis. A crystal suitable for X-ray analysis of the compound formed in DCM/EtOH at room temperature gives yellow crystal.†

(*Z*)-5-Benzylidene-2-thioxothiazolidin-4-one compound with diisopropylamine (1 : 1) (3b·HNiPr$_2$). 3b·HN·iPr$_2$ was prepared from 2-thioxothiazolidin-4-one **1**, and benzaldehyde according to the general procedure (GP3) using diisopropylamine to yield yellow crystalline materials; IR (KBr, cm^{-1}): 3454, 3028, 2970, 1738, 1430, 1366, 1225; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.38 (bs, 1H, NH), 7.51–7.44 (m, 5H, Ph), 7.18 (s, 1H, CH), 3.35 (m, 1H, CH(CH$_3$)$_2$), 1.20 (d, 6H, J = 6.6 Hz, CH(CH_3)$_2$); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 203.8, 184.4, 136.2, 135.7, 130.1, 129.5, 128.9, 124.0, 47.7, 19.3; LC/MS (ESI): 322 $[M]^+$; anal. for $C_{16}H_{22}N_2OS_2$; calcd: C, 59.59; H, 6.88; N, 8.69; found: C, 59.60; H, 6.86; N, 8.71.%

The structure **3b·HN·iPr$_2$** was confirmed by X-ray crystal structure analysis. A crystal suitable for X-ray analysis of the compound formed in DCM/EtOH at room temperature was used in the structure determination.†

(*Z*)-5-(4-Chlorobenzylidene)-2-thioxothiazolidin-4-one compound with diethylamine (1 : 1) (3c·HNEt$_2$). 3c·HNEt$_2$ was prepared from 2-thioxothiazolidin-4-one **1**, and *p*-chlorobenzaldehyde according to general procedure (GP3) to yield yellow crystalline materials; IR (KBr, cm^{-1}): 3458, 3016, 2970, 1738, 1430, 1366, 1228; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.40 (bs, 1H, NH), 7.53–7.24 (m, 5H, Ph & CH), 2.94 (q, 4H, J = 13.9 Hz, CH_2CH$_3$), 1.16 (t, 6H, J = 7.3 Hz, CH$_2$CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 196.6, 171.2, 132.6, 132.5, 130.0, 129.9, 41.9, 11.6; LC/MS (ESI): 328 $[M]^+$; anal. for $C_{14}H_{17}ClN_2OS_2$; calcd: C, 51.13; H, 5.21; N, 8.52; found: C, 51.12; H, 5.20; N, 8.50.%

The structure **3c·HNEt$_2$** was confirmed by X-ray crystal structure analysis. A crystal suitable for X-ray analysis of the compound formed in DCM/Et_2O at room temperature was used for structure determination.†

General procedure for the synthesis of 3d–g (GP4)

A mixture of aldehyde **2** (3 mmol, 318 mg), 2-thioxothiazolidin-4-one **1** (3 mmol, 400 mg), and Et_2NH (3 mmol, 310 μl) in 3 ml of degassed H_2O was stirred at room temperature for 3–5 hours until TLC showed complete disappearance of the reactants. Water (3 ml) was the added into the reaction mixture, then extracted with DCM/EtOH (3 × 50 ml) and the organic phase washed with 10% HCl (2 × 50 ml), followed by brine (2 × 50 ml), and dried over $MgSO_4$, and filtered off and evaporated to afford **3d–g**.%

(*Z*)-2-Mercapto-5-(thiophen-2-ylmethylene)thiazol-4(5*H*)-one (3d). 3d was prepared from 2-thioxothiazolidin-4-one **1**, and thiophene-2-carbaldehyde according to the general procedure (GP4) to yielding yellow powder (633 mg, 2.79 mmol, 93%). m.p: 223 °C; IR (KBr, cm^{-1}): 3456, 3018, 2970, 1738, 1430, 1366, 1228; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.88 (bs, 1H, SH), 8.05 (d, 1H, J = 5.1 Hz, thiophene), 7.88 (s, 1H, CH=), 7.68 (d, 1H, J = 2.9 Hz, thiophene), 7.28 (t, 1H, J = 3.6 Hz, thiophene); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 195.1, 169.5, 137.9, 135.9, 134.8, 129.8, 125.3, 123.5; LC/MS (ESI): 227 $[M]^+$; anal. for $C_8H_5NOS_3$; calcd: C, 42.27; H, 2.22; N, 6.16; found: C, 42.28; H, 2.20; N, 6.17.%

(*Z*)-5-(Furan-2-ylmethylene)-2-mercaptothiazol-4(5*H*)-one with (*Z*)-5-(furan-2-ylmethylene)-2-thioxothiazolidin-4-one (2 : 1) (3e). **3e** was prepared from 2-thioxothiazolidin-4-one **1**, and furan-2-carbaldehyde according to the general procedure (GP4) as brown powder (620 mg, 2.73 mmol, 91%). m.p: 150 °C; IR (KBr, cm^{-1}): 3458, 3016, 2970, 1738, 1430, 1366, 1228; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.67 (bs, 1H, SH), 8.1 (s, 1H, NH), 7.52 (d, 1H, $J = 7.3$ Hz, furan), 7.47 (s, 1H, CH═), 7.38 (t, 1H, $J =$ 7.3 Hz, furan, major isomer), 7.29 (t, 1H, $J = 7.3$ Hz, furan, minor isomer), 7.16 (d, 1H, $J = 2.9$ Hz, furan), 6.76 (bs, 1H, furan),; ^{13}C-NMR (100 MHz, DMSO-d_{63}): $\delta = 197.7$, 169.7, 150.0, 148.8, 136.3, 130.0, 128.1, 127.7, 123.2, 120.3, 118.1, 114.4; LC/MS (ESI): 210 $[M]^+$; anal. for $C_8H_5NO_2S_2$; calcd: C, 45.48; H, 2.39; N, 6.63; found: C, 45.44; H, 2.42; N, 6.61.%

(*Z*)-5-((1*H*-Pyrrol-2-yl)methylene)-2-mercaptothiazol-4(5*H*)-one (3f). **3f** was prepared from 2-thioxothiazolidin-4-one **1**, and 1*H*-pyrrole-2-carbaldehyde according to the general procedure (GP4) to yielding crimson powder (598 mg, 2.85 mmol, 95%). m.p: 220 °C; IR (KBr, cm^{-1}): 3458, 3016, 2970, 1738, 1430, 1366, 1228; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.54 (bs, 1H, SH), 11.80 (s, 1H, NH), 7.50 (s, 1H, CH═), 7.28 (bs, 1H, Pyrrol), 6.52 (bs, 1H, Pyrrol), 6.39 (bs, 1H, Pyrrol); ^{13}C-NMR (100 MHz, DMSO-d_6): $\delta = 195.3$, 169.7, 127.7, 126.3, 122.5, 117.4, 115.5, 113.3; LC/MS (ESI): 210 $[M]^+$; anal. for $C_8H_6N_2OS_2$; calcd: C, 45.69; H, 2.88; N, 13.32; found: C, 45.72; H, 2.90; N, 13.33.%

(*Z*)-2-Mercapto-5-(pyridin-2-ylmethylene)thiazol-4(5*H*)-one (3g). **3g** was prepared from 2-thioxothiazolidin-4-one **1**, and picolinaldehyde according to the general procedure (GP4) to yielding yellow needle (599 mg, 2.7 mmol, 90%). m.p: 210 °C; IR (KBr, cm^{-1}): 3458, 3016, 2970, 1738, 1430, 1366, 1228; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.66 (bs, 1H, SH), 8.78 (d, 1H, $J = 5.1$ Hz, Pyridine), 7.94–7.90 (m, 2H, Pyridine), 7.67 (s, 1H, CH═), 7.43 (t, 1H, $J = 1.9$ Hz, Pyridine); ^{13}C-NMR (100 MHz, DMSO-d_6): $\delta = 202.5$, 169.8, 151.6, 150.0, 138.1, 130.2, 128.7, 127.9, 124.5; LC/MS (ESI): 222 $[M]^+$; anal. for $C_9H_6N_2OS_2$; calcd: C, 48.63; H, 2.72; N, 12.60; found: C, 48.62; H, 2.72; N, 12.61.%

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