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Different N–C–N formation reactions of aromatic aldehydes and thiohydantoins controlled by Lewis acid promoters

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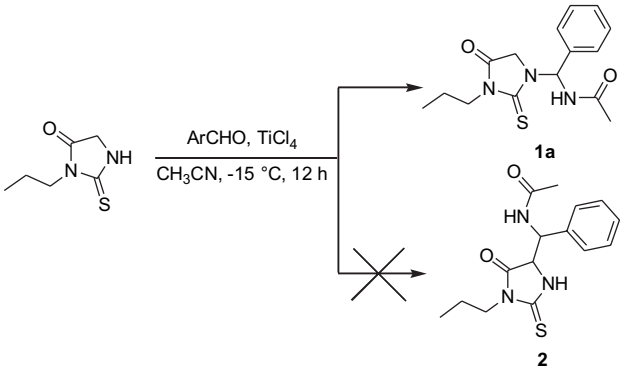
Abstract—A three-component reaction of aromatic aldehydes, acetonitrile, and 2-thiohydantoins promoted by $TiCl_4$ was discovered, and a different N–C–N bond-forming reaction took place with $FeCl_3$, $AlCl_3$ or $BF_3 \cdot Et_2O$ as promoter. The thiohydantoin derivatives **1** and **3** were synthesized in moderate to high yields. A plausible mechanism for the formation of **1** and **3** is suggested.

1. Introduction

Multicomponent reactions (MCRs) have attracted considerable academic and industrial interest along with enormous demands on the number and quality of compounds for drug discovery.[1] The development of new MCRs will offer efficient and convenient entries into interesting structures.

Thiohydantoins and their derivatives exist in many fungicides, herbicides, medicines, and natural products.[2] Great efforts have been devoted to introducing thiohydantoins and their derivatives into desirable substrates such as pharmacophores and synthetic intermediates in the past decades.[3] For example, Roué and Bergman reported the synthesis of the marine alkaloid leucettamine B from the thiohydantoin derivatives.[4] Jakše et al. presented a few examples of synthesizing aplysinopsin analogues with 5-dimethylaminomethyldiene-2-thiohydantoin as the key intermediate.[5] Chérouvrier et al. developed a straightforward access to new alkylaminomethylidene derivatives of 2-thiohydantoins via the eco-friendly solventless methodology assisted with microwave heating.[6] *S*-Methylated *N*-benzoylthiohydantoin was designed as a new ring precursor to synthesize the marine sponge alkaloids, (*Z*)-hymenialdisine and (*Z*)-2-debromohymenialdisine.[7]

In our recent experiments, a new kind of product **1** was obtained accidentally in the course of looking for some thiohydantoin derivatives **2** as synthetic intermediates of pharmacophores (Scheme 1). The 5-C and 2-S of thiohydantoins are typical nucleophilic positions, and condensation of aldehydes and thiohydantoins to get 5-C unsaturated thiohydantoin derivatives has become an important reaction.[3–6,8] It seems possible to construct **2** via MCRs under some conditions. So we carried out the reaction of 3-propyl-2-thiohydantoin and benzaldehyde in acetonitrile with titanium tetrachloride as promoter. Surprisingly, **1a** was obtained in a moderate yield with 1-N of 3-propyl-2-thiohydantoin as nucleophilic position. To the best of our knowledge, there have been no reports on this type of reactions. Most of the



Scheme 1.

Keywords: 2-Thiohydantoins; Lewis acids; Multicomponent reactions.
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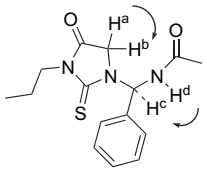
1-substituted thiohydantoins are usually synthesized through the route: *N*-substituted-amino acids or esters react with isothiocyanates to yield thioureas, which are then cyclized to the thiohydantoins.[9] It was also reported that 1-acetyl-2-thiohydantoin was synthesized from amino acid under acylation conditions.[8c,10] As a result, we have discovered a new N–C–N bond-forming MCR with $TiCl_4$ as promoter, and then another different reaction with $FeCl_3$, $AlCl_3$ and $BF_3{\cdot}Et_2O$ as promoters. Herein, we wish to describe our results of MCR with thiohydantoins.

2. Results and discussion

Initially, we carried out the three-component reaction of 3-propyl-2-thiohydantoin, benzaldehyde, and acetonitrile (reagent as well as solvent) at room temperature with $TiCl_4$ as promoter. There were many products indicated by TLC. However, no product **1a** could be isolated (Table 1, entries 1–4). Further experiments to separate and identify are not successful. With several trials, we found that temperature is a key factor. Lowering the temperature to −15 °C, the reaction of 3-propyl-2-thiohydantoin, 1.1 equiv of benzaldehyde, and 1.2 equiv of $TiCl_4$ in acetonitrile for 12 h gave the corresponding product **1a** in a moderate yield (53%) (Table 1, entry 6). Other factors were further investigated. Product **1a** was got in good to high yields by adjusting the ratio of 3-propyl-2-thiohydantoins to benzaldehyde as 2:1 (Table 1, entries 7–11).

In the 300 MHz ^1H NMR spectrum of product **1a** dissolved in DMSO-d_6, the doublet of doublets at δ 4.22 ppm is attributed to H^a and H^b. The two doublets at 7.51 ppm and 8.96 ppm are attributed to H^c and H^d, respectively (Fig. 1).



1a

Figure 1. ^1H–^1H coupling relations of **1a**.

After adding D_2O to DMSO-d_6, H^c displayed a single peak at 7.49 ppm, and H^d as an active proton displayed a small doublet at 8.98 ppm due to incomplete exchange with deuterium of D_2O, confirming the attribution of the peaks.

The structure of **1a** (obtained by the slow evaporation in petroleum ether and ethyl acetate) was further confirmed by X-ray single-crystal analysis (Fig. 2).[11]

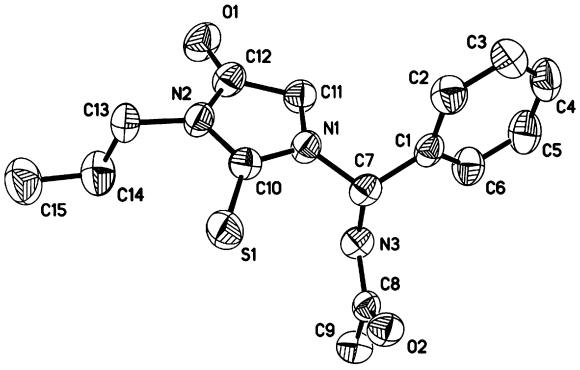
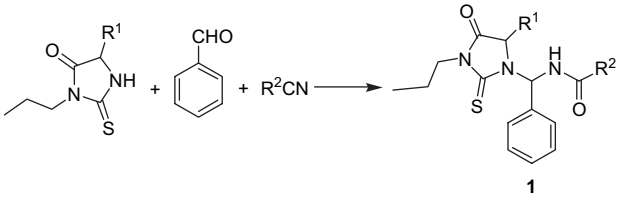
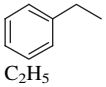


Figure 2. X-ray structure of compound **1a**.

Table 1. $TiCl_4$-promoted reactions of 2-thiohydantoins, aromatic aldehydes, and nitrile



1

Entry	R^1	R^2	Temperature (°C)	Ratio (2-thiohydantoins–C_6H_5CHO–$TiCl_4$)	Time (h)	Product	Yield[a] (%)
1	H	CH_3	rt	1:1.1:1.2	12	**1a**	0
2	H	CH_3	rt	1:1.1:2.4	12	**1a**	0
3	H	CH_3	rt	1:2.2:2.4	12	**1a**	0
4	H	CH_3	rt	1:1.1:3.6	12	**1a**	0
5	H	CH_3	0	1:1.1:1.2	12	**1a**	35
6	H	CH_3	−15	1:1.1:1.2	12	**1a**	53
7	H	CH_3	−15	1.5:1:1.2	12	**1a**	75
8	H	CH_3	−15	2:1:1.2	12	**1a**	81
9	H	CH_3	−15	3:1:1.2	12	**1a**	80
10	H	CH_3	−15	2:1:1.2	24	**1a**	80
11	H	CH_3	−40	2:1:1.2	24	**1a**	81
12	H	$H_2C{=}C(H)-$	−15	2:1:1.2	12		0
13	H		−15	2:1:1.2	12		0
14	H	C_2H_5	−15	2:1:1.2	12		Trace[b]
15	CH_3	CH_3	−15	1:1.1:1.2	12	**1q**	16
16	CH_3	CH_3	−15	2:1:1.2	12	**1q**	34

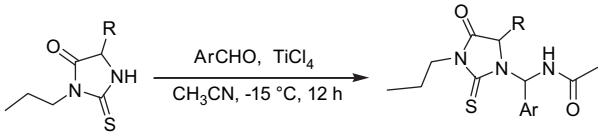
[a] Isolated yields from silica gel chromatography.
[b] Isolation failed.

Meanwhile, the extension of the scope of this new procedure was explored. Product **1q** was obtained in low yields (16%) (Table 1, entry 15). By adjusting the ratio of 5-methyl-3-propyl-2-thiohydantoins to benzaldehyde as 2:1, inspite of the yield having been improved twice, it was still not very satisfactory (Table 1, entry 16). This may be caused by the steric effect of the substituent on the 5-C of thiohydantoin. We also noted that the corresponding products were not obtained in phenylacetonitrile and acrylonitrile (reagent as well as solvent) instead of acetonitrile (Table 1, entries 12 and 13). Trace of uncertain product was detected in propionitrile through TLC, but the product was not successfully isolated (Table 1, entry 14).

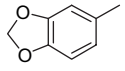
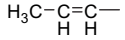
Various aldehydes were also examined under the conditions for entry 8 of Table 1, and the results are summarized in Table 2 (entries 1–24). For 3-propyl-2-thiohydantoin, the yields of products **1** were obtained from 51% to 90% (Table 2, entries 1–16), and the corresponding products **1** were not obtained with 3-pyridinecarboxaldehyde, 2-furaldehyde, and crotonaldehyde (Table 2, entries 17–19). For 5-methyl-3-propyl-2-thiohydantoin, low yields of products **1** were in the range of 10–47% (Table 2, entries 20–24).

Subsequently, other Lewis acids such as $FeCl_3\cdot 6H_2O$, $SnCl_4\cdot 5H_2O$, $ZrOCl_2\cdot 8H_2O$, $Ti[OCH(CH_3)_2]_4$, $FeCl_3$, $AlCl_3$, and $BF_3\cdot Et_2O$ were also examined. In the cases of $FeCl_3$, $AlCl_3$, and $BF_3\cdot Et_2O$, **1** was not obtained but **3** was obtained as the sole product whose structure was examined with spectroscopic analysis. The structure of **3d** (obtained by the slow evaporation in ethyl acetate, ethanol, and acetone) was finally confirmed by X-ray single-crystal analysis (Fig. 3).[12] In this way, a new N–C–N bond-forming reaction was discovered as shown in Table 3.

Table 2. $TiCl_4$-promoted reactions of 2-thiohydantoins, aromatic aldehydes, and acetonitrile



1

Entry	R	Ar	Product	Yield[a] (%)
1	H	C_6H_5	**1a**	81
2	H	4-$NO_2C_6H_4$	**1b**	80
3	H	3-$NO_2C_6H_4$	**1c**	74
4	H	4-ClC_6H_4	**1d**	90
5	H	3-ClC_6H_4	**1e**	80
6	H	2-ClC_6H_4	**1f**	56
7	H	2,4-$Cl_2C_6H_3$	**1g**	64
8	H	4-FC_6H_4	**1h**	85
9	H	3-FC_6H_4	**1i**	84
10	H	2-FC_6H_4	**1j**	71
11	H	4-$CH_3C_6H_4$	**1k**	75
12	H	3-$CH_3C_6H_4$	**1l**	87
13	H	2-$CH_3C_6H_4$	**1m**	56
14	H	4-$CH_3OC_6H_4$	**1n**	51
15	H	2-$CH_3OC_6H_4$	**1o**	65
16	H		**1p**	57
17	H			0
18	H			0
19	H			0
20	CH_3	C_6H_5	**1q**	34
21	CH_3	4-$NO_2C_6H_4$	**1r**	47
22	CH_3	3-$NO_2C_6H_4$	**1s**	30
23	CH_3	4-ClC_6H_4	**1t**	31
24	CH_3	4-$CH_3OC_6H_4$	**1u**	10

[a] Isolated yields from silica gel chromatography.

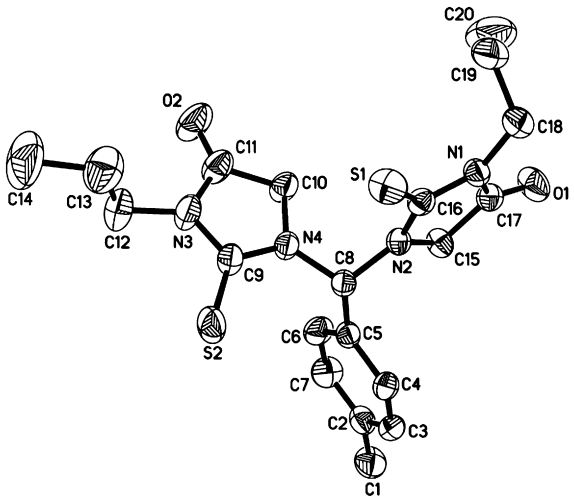


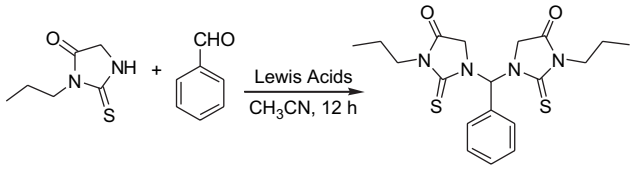
Figure 3. X-ray structure of compound **3d**.

On the basis of the structure of **3**, we modulated the ratio of the substrates to the promoters $AlCl_3$ and $BF_3\cdot Et_2O$. Benzaldehyde, 2 equiv of 3-propyl-2-thiohydantoin, and 1.2 equiv of $AlCl_3$ in acetonitrile reacted for 12 h, affording **3a** in an isolated yield of 31% (Table 3, entry 6). Prolonging the reaction time did not increase the yield. At room temperature, the yield was only 6% (Table 3, entry 9), while no other byproduct was shown. To improve the yields, we increased the amount of 3-propyl-2-thiohydantoin to 6 equiv and got a moderate yield of product **3a** (Table 3, entry 8). Although excess 3-propyl-2-thiohydantoin was used, over 90% can be recovered. We also noted that $BF_3\cdot Et_2O$ is a better promoter than $AlCl_3$ and $FeCl_3$. With $BF_3\cdot Et_2O$ as promoter and a slight excess of 3-propyl-2-thiohydantoin, product **3a** was obtained in high yield (81%) (Table 3, entry 12).

Then various arylaldehydes were examined under the above-mentioned conditions (Table 3, entry 12) with $BF_3\cdot Et_2O$ as promoter and the results are summarized in Table 4 (entries 1–5).

To extend the applied range of the three-component reaction, 3-methyl-2-pyrazolin-5-one, 2-imidazolidone, 2-imidazolidinethione, thiourea, caprolactam, and *N*-(*p*-tolylcarbamothioyl) benzamide as other types of substrates were tested using $TiCl_4$ as promoter (Scheme 2 and Table 5). Similar reaction occurred in low yields using 2-imidazolidinethione with acetonitrile and propionitrile as reagent and solvent (Table 5, entries 1 and 2), and it did not occur in phenylacetonitrile. The NH group may be activated by the C=S moiety in 2-imidazolidinethione and thiohydantoins comparing to NH group of amide. As for *N*-(*p*-tolylcarbamothioyl) benzamide and thiourea, the reaction did not occur that may be affected by the steric effect and the nucleophilicity of NH group.

Table 3. Other Lewis acids-promoted reactions of 2-thiohydantoins and aromatic aldehydes

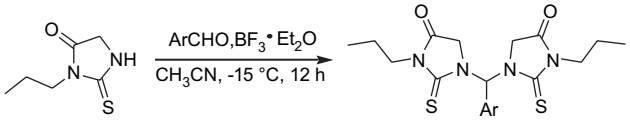


3

Entry	Lewis acids	Temperature (°C)	Ratio (2-thiohydantoins–C_6H_5CHO–Lewis acids)	Product[a] (%)	
				1a	**3a**
1	$FeCl_3\cdot 6H_2O$	−15	2:1:1.2	0	0
2	$SnCl_4\cdot 5H_2O$	−15	2:1:1.2	0	0
3	$ZrOCl_2\cdot 8H_2O$	−15	2:1:1.2	0	0
4	$Ti[OCH(CH_3)_2]_4$	−15	2:1:1.2	0	0
5	$FeCl_3$	−15	2:1:1.2	0	35
6	$AlCl_3$	−15	2:1:1.2	0	31
7	$AlCl_3$	−15	4:1:1.2	0	43
8	$AlCl_3$	−15	6:1:1.2	0	61
9	$AlCl_3$	rt	2.2:1:1.2	0	6
10	$BF_3\cdot Et_2O$	0	2:1:1.2	0	55
11	$BF_3\cdot Et_2O$	−15	2:1:1.2	0	74
12	$BF_3\cdot Et_2O$	−15	2.4:1:1.2	0	81

[a] Isolated yields from silica gel chromatography.

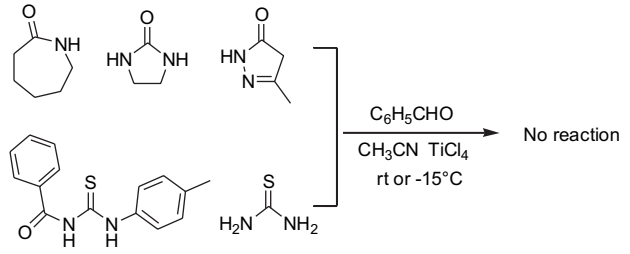
Table 4. $BF_3\cdot Et_2O$-promoted reactions of 3-propyl-2 thiohydantoin and aromatic aldehydes



3

Entry	Ar	Product	Yield[a] (%)
1	C_6H_5	**3a**	81
2	4-ClC_6H_4	**3b**	60
3	3-ClC_6H_4	**3c**	61
4	4-$CH_3C_6H_4$	**3d**	88
5	4-$CH_3OC_6H_4$	**3e**	44

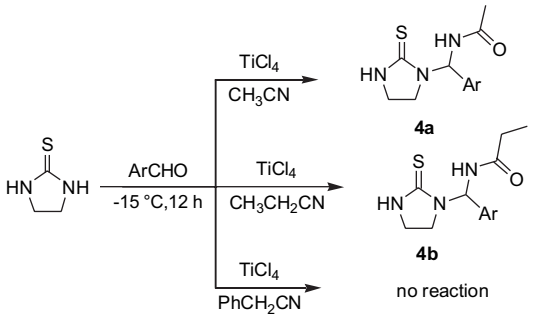
[a] Isolated yields from silica gel chromatography.



Scheme 2.

All results described above indicated that $TiCl_4$ and $BF_3\cdot Et_2O$ play different roles as Lewis acid promoters. The Lewis acidity[13] and/or ability of forming coordination intermediate[14] may be the reason for the two different pathways. Two plausible mechanisms were proposed for $TiCl_4$- and $BF_3\cdot Et_2O$-promoted reaction, respectively, as shown in Schemes 3 and 4. In the case of $TiCl_4$ as promoter, an adduct was first formed and then converted to the carbocation intermediate **A**. Products **1** are obtained via the trapping of carbocation **A** by the nitrile as that in the Ritter reaction.[15] In the case of $BF_3\cdot Et_2O$, carbocation **A** was also formed and trapped by another 3-propyl-2-thiohydantoin molecule, then products **3** were formed subsequently.[16]

Table 5. $TiCl_4$-promoted reactions of 2-imidazolidinethione, aromatic aldehydes, and nitriles

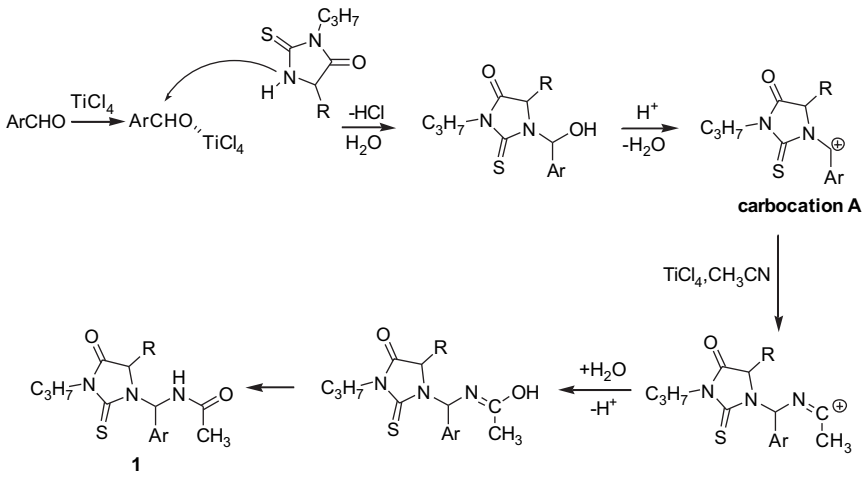


Entry	Ar	Ratio (2-imidazolidinethione–ArCHO–$TiCl_4$)	Product	Yield[a] (%)
1	C_6H_5	1.2:1:1.2	**4a**	24
2	4-ClC_6H_4	1.2:1:1.2	**4b**	13

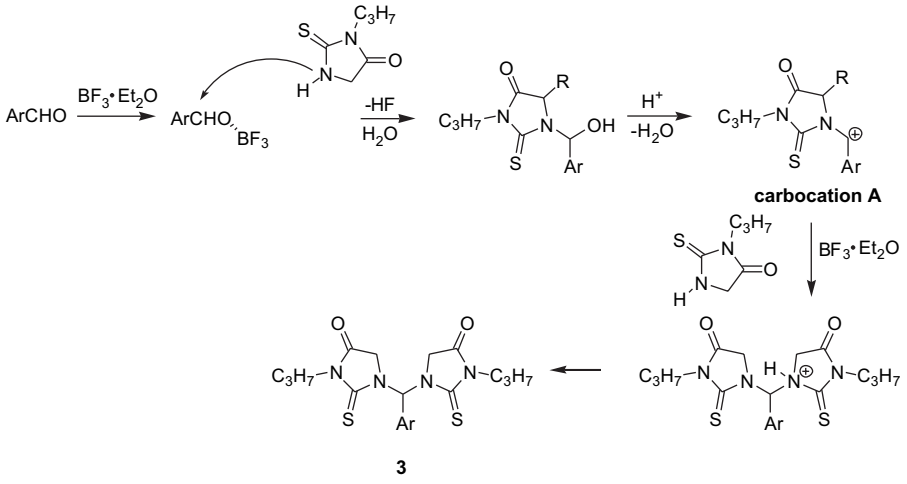
[a] Isolated yields from silica gel chromatography.

3. Conclusion

To summarize, we have developed two MCRs of 2-thiohydantoins promoted by $TiCl_4$ or $BF_3\cdot Et_2O$. Under mild reaction conditions, the amidals **1** or **3** were obtained in moderate to high yields. Further investigations on the scope and application of the protocol and products are in progress.



Scheme 3. Proposed mechanism of $TiCl_4$-promoted reaction of 2-thiohydantoin, aromatic aldehyde, and acetonitrile.



Scheme 4. Proposed mechanism of $BF_3 \cdot Et_2O$-promoted reaction of 2-thiohydantoin and aromatic aldehyde.

4. Experimental

4.1. General information

The reagents and solvents were commercially available and used without further treatment unless indicated. 3-Propyl-2-thiohydantoin and 3-propyl-5-methyl-2-thiohydantoin were synthesized according to the literature procedure.[6]

^1H NMR and ^{13}C NMR spectra of synthesized compounds were obtained on a 300 MHz NMR Mercury-300 B (Varian) and 400 MHz NMR (Bruker) using tetramethylsilane as an internal standard. Mass spectra were recorded on an Applied Biosystem Q-Trap triple quadrupole mass spectrometer (Applied Biosystems Sciex, Foster City, USA) equipped with an electrospray ionization (ESI) source. IR spectra (KBr) were obtained on a Nicolet 5700 FT-IR spectrophotometer (Thermo). The X-ray single-crystal structure analysis of **1a** was performed on a Rigaku R-AXIS RAPID diffractometer (Mo Kα radiation, λ=0.71073 Å, graphite monochromator) in the ψ rotation scan mode. The X-ray single-crystal structure analysis of **3d** was performed on a Bruker Apex CCD diffractometer with graphite-monochromated Mo Kα radiation (λ=0.71069 Å). Elemental analysis was performed on a Perkin–Elmer 240-C instrument. Melting points were measured on a Pekin-X4 apparatus without correction.

4.2. General procedure for the synthesis of compounds 1

To a stirred solution of 3-propyl-2-thiohydantoin or 5-methyl-3-propyl-2-thiohydantoin (2 mmol) and aromatic aldehydes (1 mmol) in CH_3CN (8 mL), $TiCl_4$ (1.2 mmol) was added at −15 °C. The reaction mixture was stirred for 12 h at the same temperature. By adding a saturated $NaHCO_3$ aqueous solution, the reaction was quenched. The mixture was extracted with ethyl acetate (20 mL×2) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by column chromatography on silica gel (petroleum ether–EtOAc, 1:2) to give compound **1**.

4.2.1. Compound 1a. White solid, mp 156–158 °C; IR (KBr) 3277, 2966, 2938, 1745, 1653, 1541, 1348, 1204, 1116 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.4 Hz, 3H), 1.57–1.62 (m, 2H), 1.97 (s, 3H), 3.66 (t, J=7.4 Hz, 2H), 4.07 (dd, J=19.5 Hz, 2H), 7.30–7.41 (m, 5ArH), 7.51 (d, J=8.4 Hz, 1H), 8.97 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.4, 42.5,

48.4, 62.4, 126.4, 128.3, 128.7, 136.5, 169.3, 170.7, 182.0; MS (ESI): m/z=328.1 $[M+Na]^+$, 633.2 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76. Found: C, 58.87; H, 6.29; N, 13.55.

4.2.2. Compound 1b. White solid, mp 151–152 °C; IR (KBr) 3308, 2974, 2935, 1746, 1681, 1520, 1462, 1349, 1218, 1128 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.7 Hz, 3H), 1.57–1.62 (m, 2H), 1.98 (s, 3H), 3.66 (t, J=7.2 Hz, 2H), 4.13 (dd, J=19.5 Hz, 2H), 7.56 (d, J=8.4 Hz, 1H), 7.62 (d, J=8.7 Hz, 2ArH), 8.24 (d, J=8.7 Hz, 2ArH), 9.11 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.4, 42.7, 48.6, 62.0, 123.8, 128.0, 143.9, 147.4, 169.5, 170.7, 182.3; MS (ESI): m/z=373.1 $[M+Na]^+$, 723.1 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{18}N_4O_4S$: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.53; H, 5.24; N, 15.93.

4.2.3. Compound 1c. White solid, mp 174–176 °C; IR (KBr) 3326, 2971, 2936, 1736, 1680, 1529, 1465, 1349, 1217, 1127, 687 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.5 Hz, 3H), 1.58–1.65 (m, 2H), 2.00 (s, 3H), 3.67 (t, J=7.4 Hz, 2H), 4.13 (dd, J=19.5 Hz, 2H), 7.59 (d, J=8.4 Hz, 1ArH), 7.71 (t, J=7.8 Hz, 1ArH), 7.82 (d, J=7.8 Hz, 1ArH), 8.15 (s, 1ArH), 8.22 (d, J=7.5 Hz, 1H), 9.13 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.5, 42.7, 48.6, 61.9, 121.4, 123.4, 130.4, 133.3, 138.7, 148.1, 169.6, 170.8, 182.3; MS (ESI): m/z=373.1 $[M+Na]^+$, 723.2 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{18}N_4O_4S$: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.40; H, 5.22; N, 15.97.

4.2.4. Compound 1d. White solid, mp 161–163 °C; IR (KBr) 3270, 2978, 2934, 1753, 1687, 1521, 1469, 1354, 1227, 1123, 856, 688 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.5 Hz, 3H), 1.56–1.64 (m, 2H), 1.96 (s, 3H), 3.65 (t, J=7.4 Hz, 2H), 4.08 (dd, J=19.5 Hz, 2H), 7.35 (d, J=8.7 Hz, 2ArH), 7.46 (d, J=8.7 Hz, 2ArH, 1CH–Ar), 8.97 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.4, 42.6, 48.4, 61.9, 128.4, 128.6, 132.9, 135.6, 169.3, 170.7, 182.0; MS (ESI): m/z=362.5 $[M+Na]^+$, 702.0 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{18}ClN_3O_2S$: C, 53.01; H, 5.34; N, 12.36. Found: C, 53.11; H, 5.37; N, 12.20.

4.2.5. Compound 1e. White solid, mp 121–122 °C; IR (KBr) 3321, 2970, 1747, 1679, 1507, 1470, 1356, 1220, 1128, 690 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.5 Hz, 3H), 1.56–1.62 (m, 2H), 1.97 (s, 3H), 3.66 (t, J=7.4 Hz, 2H), 4.09 (dd, J=19.5 Hz, 2H), 7.30–7.48 (m, 4ArH, 1CH–Ar), 9.00 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.4, 42.6, 48.5, 62.0, 125.3, 126.3, 128.3, 130.6, 133.5, 139.0, 169.4, 170.8, 182.1; MS (ESI): m/z=362.0 $[M+Na]^+$, 701.1 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{18}ClN_3O_2S$: C, 53.01; H, 5.34; N, 12.36. Found: C, 53.15; H, 5.29; N, 12.45.

4.2.6. Compound 1f. White solid, mp 154–156 °C; IR (KBr) 3305, 2976, 1752, 1652, 1538, 1455, 1359, 1223, 1128 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.85 (t, J=7.5 Hz, 3H), 1.56–1.61 (m, 2H), 1.92 (s, 3H), 3.65 (t, J=7.4 Hz, 2H), 4.12 (dd, J=19.5 Hz, 2H), 7.31–7.52 (m, 4ArH, 1CH–Ar), 8.86 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 20.5, 22.2, 42.4, 49.7, 61.7, 127.4, 128.1, 129.9, 130.1, 132.3, 134.5, 169.1, 170.7, 181.6; MS (ESI): m/z=362.0 $[M+Na]^+$, 701.0 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{18}ClN_3O_2S$: C, 53.01; H, 5.34; N, 12.36. Found: C, 52.97; H, 5.45; N, 12.29.

4.2.7. Compound 1g. White solid, mp 191–192 °C; IR (KBr) 3315, 2967, 2935, 1748, 1655, 1537, 1447, 1351, 1217, 1125, 674 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.85 (t, J=7.4 Hz, 3H), 1.55–1.63 (m, 2H), 1.92 (s, 3H), 3.65 (t, J=7.4 Hz, 2H), 4.14 (dd, J=19.5 Hz, 2H), 7.27 (d, J=7.5 Hz, 1H), 7.43 (dd, J=1.8, 8.4 Hz, 1ArH), 7.52 (d, J=8.4 Hz, 1ArH), 7.68 (d, J=1.8 Hz, 1ArH), 8.87 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 20.5, 22.2, 42.4, 49.7, 61.3, 127.4, 129.3, 129.5, 133.3, 133.8, 133.8, 169.2, 170.7, 181.7; MS (ESI): m/z=396.1 $[M+Na]^+$, 771.1 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{17}Cl_2N_3O_2S$: C, 48.14; H, 4.58; N, 11.23. Found: C, 48.19; H, 4.67; N, 11.18.

4.2.8. Compound 1h. White solid, mp 139–141 °C; IR (KBr) 3274, 2956, 1753, 1686, 1510, 1470, 1354, 1224, 1122 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.5 Hz, 3H), 1.57–1.64 (m, 2H), 1.96 (s, 3H), 3.65 (t, J=7.4 Hz, 2H), 4.08 (dd, J=19.5 Hz, 2H), 7.20–7.40 (m, 4ArH), 7.47 (d, J=8.4 Hz, 1H), 8.96 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.4, 42.5, 48.35, 61.9, 115.4 (d, J=21.9 Hz), 128.6 (d, J=8.0 Hz), 132.7 (d, J=3.5 Hz), 161.9 (d, J=243.9 Hz), 169.3, 170.7, 182.0; MS (ESI): m/z=346.4 $[M+Na]^+$, 669.6 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{18}FN_3O_2S$: C, 55.71; H, 5.61; N, 12.99. Found: C, 55.64; H, 5.70; N, 12.91.

4.2.9. Compound 1i. White solid, mp 140–141 °C; IR (KBr) 3290, 2961, 2930, 1754, 1686, 1514, 1467, 1392, 1223, 1121, 805 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.5 Hz, 3H), 1.57–1.65 (m, 2H), 1.97 (s, 3H), 3.66 (t, J=7.5 Hz, 2H), 4.09 (dd, J=19.2 Hz, 2H), 7.16–7.22 (m, 3ArH), 7.44–7.50 (m, 1ArH, 1CH–Ar), 8.98 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.4, 42.6, 48.4, 61.9, 113.5 (d, J=23.0 Hz), 115.1 (d, J=20.7 Hz), 122.6 (d, J=2.3 Hz), 130.7 (d, J=8.1 Hz), 139.4 (d, J=6.9 Hz), 162.3 (d, J=244.1 Hz), 169.4, 170.7, 182.1; MS (ESI): m/z=346.1 $[M+Na]^+$, 669.2 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{18}FN_3O_2S$: C, 55.71; H, 5.61; N, 12.99. Found: C, 55.80; H, 5.58; N, 12.93.

4.2.10. Compound 1j. White solid, mp 138–140 °C; IR (KBr) 3328, 2969, 1753, 1672, 1528, 1470, 1359, 1128 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.85 (t, J=7.4 Hz, 3H), 1.55–1.63 (m, 2H), 1.92 (s, 3H), 3.64 (t, J=7.4 Hz, 2H), 4.17 (dd, J=19.5 Hz, 2H), 7.19–7.27 (m, 2ArH), 7.46–7.39 (m, 2ArH, 1CH–Ar), 8.94 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 20.4, 22.2, 42.4, 49.4, 58.7, 115.7 (d, J=20.7 Hz), 124.2 (d, J=12.7 Hz), 124.5 (d, J=2.3 Hz), 128.3 (d, J=3.5 Hz), 130.5 (d, J=8.1 Hz), 159.6 (d, J=247.4 Hz), 169.1, 170.6, 181.5; MS (ESI): m/z=346.3 $[M+Na]^+$, 669.4 $[2M+Na]^+$. Anal. Calcd for $C_{15}H_{18}FN_3O_2S$: C, 55.71; H, 5.61; N, 12.99. Found: C, 55.75; H, 5.56; N, 13.03.

4.2.11. Compound 1k. White solid, mp 134–136 °C; IR (KBr) 3268, 2952, 1747, 1686, 1525, 1352, 1122,

691 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.4 Hz, 3H), 1.58–1.61 (m, 2H), 1.96 (s, 3H), 2.30 (s, 3H), 3.65 (t, J=7.4 Hz, 2H), 4.05 (dd, J=19.5 Hz, 2H), 7.20 (s, 4ArH), 7.46 (d, J=8.7 Hz, 1H), 8.90 (d, J=8.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 20.6, 22.4, 42.5, 48.3, 62.2, 126.3, 129.2, 133.6, 137.6, 169.2, 170.7, 181.9; MS (ESI): m/z=342.5 $[M+Na]^+$, 661.7 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16. Found: C, 60.23; H, 6.58; N, 13.24.

4.2.12. Compound 1l. White solid, mp 99–101 °C; IR (KBr) 3282, 2968, 1750, 1647, 1540, 1451, 1355, 1226, 1122 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.4 Hz, 3H), 1.59–1.62 (m, 2H), 1.96 (s, 3H), 2.32 (s, 3H), 3.66 (t, J=7.2 Hz, 2H), 4.08 (dd, J=19.5 Hz, 2H), 7.11–7.29 (m, 4ArH), 7.46 (d, J=8.4 Hz, 1H), 8.92 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 21.0, 22.4, 42.5, 48.4, 62.4, 123.5, 126.9, 128.6, 128.9, 136.5, 138.0, 169.2, 170.7, 181.9; MS (ESI): m/z=342.5 $[M+Na]^+$, 661.7 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16. Found: C, 60.10; H, 6.69; N, 13.10.

4.2.13. Compound 1m. White solid, mp 184–186 °C; IR (KBr) 3292, 2959, 1751, 1651, 1548, 1409, 1353, 1214, 1126 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.85 (t, J=7.5 Hz, 3H), 1.56–1.63 (m, 2H), 1.92 (s, 3H), 2.34 (s, 3H), 3.65 (t, J=7.5 Hz, 2H), 4.06 (dd, J=19.8 Hz, 2H), 7.20–7.33 (m, 4ArH, 1CH–Ar), 8.82 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 18.5, 20.4, 22.1, 42.3, 49.5, 61.2, 125.6, 126.0, 128.2, 130.6, 135.2, 135.8, 168.9, 170.7, 181.6; MS (ESI): m/z=342.1 $[M+Na]^+$, 661.1 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16. Found: C, 60.19; H, 6.56; N, 13.09.

4.2.14. Compound 1n. White solid, mp 146–148 °C; IR (KBr) 3270, 2964, 1757, 1684, 1517, 1471, 1227, 1123 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.5 Hz, 3H), 1.58–1.61 (m, 2H), 1.95 (s, 3H), 3.65 (t, J=7.4 Hz, 2H), 3.75 (s, 3H), 4.04 (dd, J=19.4 Hz, 2H), 6.95 (d, J=8.7 Hz, 2ArH), 7.24 (d, J=8.7 Hz, 2ArH), 7.43 (d, J=8.4 Hz, 1H), 8.87 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.4, 42.5, 48.3, 55.2, 62.1, 114.0, 127.7, 128.4, 159.2, 169.2, 170.7, 181.8; MS (ESI): m/z=358.5 $[M+Na]^+$, 693.2 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_3S$: C, 57.29; H, 6.31; N, 12.53. Found: C, 57.34; H, 6.40; N, 12.48.

4.2.15. Compound 1o. White solid, mp 187–189 °C; IR (KBr) 3307, 2975, 1749, 1652, 1541, 1463, 1352, 1254, 1125 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.84 (t, J=7.5 Hz, 3H), 1.55–1.62 (m, 2H), 1.91 (s, 3H), 3.64 (t, J=7.1 Hz, 2H), 3.78 (s, 3H), 4.03 (dd, J=19.5 Hz, 2H), 6.95 (t, J=7.2 Hz, 1ArH), 7.05 (d, J=8.1 Hz, 1ArH), 7.28–7.35 (m, 2ArH, 1CH–Ar), 8.67 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 20.5, 22.3, 42.3, 49.7, 55.6, 60.2, 111.4, 120.2, 124.6, 127.5, 129.9, 156.7, 168.9, 170.7, 181.4; MS (ESI): m/z=358.4 $[M+Na]^+$, 693.2 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_3S$: C, 57.29; H, 6.31; N, 12.53. Found: C, 57.36; H, 6.36; N, 12.57.

4.2.16. Compound 1p. White solid, mp 120–121 °C; IR (KBr) 3279, 2968, 2883, 1758, 1678, 1505, 1466, 1352, 1256, 1122, 1042 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.2 Hz, 3H), 1.56–1.63 (m, 2H), 1.95 (s, 3H), 3.64 (t, J=7.4 Hz, 2H), 4.06 (dd, J=19.5 Hz, 2H), 6.03 (s, 2H), 6.81 (d, J=8.1 Hz, 1ArH), 6.92 (d, J=7.8 Hz, 2ArH), 7.39 (d, J=8.1 Hz, 1H), 8.87 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.5, 22.4, 42.5, 48.3, 62.3, 101.3, 107.0, 108.2, 120.0, 130.4, 147.2, 147.6, 169.2, 170.7, 181.8; MS (ESI): m/z=372.1 $[M+Na]^+$, 721.2 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{19}N_3O_4S$: C, 55.00; H, 5.48; N, 12.03. Found: C, 55.07; H, 5.54; N, 12.11.

4.2.17. Compound 1q. White solid, mp 146–148 °C; IR (KBr) 3268, 2963, 2933, 1747, 1665, 1551, 1421, 1353, 1132, 1046, 751 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.5 Hz, 3H), 1.11 (d, J=6.9 Hz, 3H), 1.62–1.64 (m, 2H), 2.02 (s, 3H), 3.69 (t, J=7.1 Hz, 2H), 4.31 (q, J=6.9 Hz, 1H), 7.34–7.39 (m, 5ArH), 7.52 (d, J=8.7 Hz, 1H), 9.07 (d, J=8.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 16.3, 20.5, 22.3, 42.6, 55.6, 62.8, 126.1, 128.0, 128.3, 137.5, 169.9, 174.1, 182.3; MS (ESI): m/z=342.1 $[M+Na]^+$, 661.3 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16. Found: C, 60.21; H, 6.69; N, 13.10.

4.2.18. Compound 1r. White solid, mp 176–178 °C; IR (KBr) 3262, 2964, 2931, 1749, 1668, 1525, 1418, 1352, 1135 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.88 (t, J=7.5 Hz, 3H), 1.17 (d, J=6.9 Hz, 3H), 1.60–1.67 (m, 2H), 2.05 (s, 3H), 3.70 (t, J=7.4 Hz, 2H), 4.39 (q, J=6.9 Hz, 1H), 7.59 (d, J=8.4 Hz, 1H), 7.66 (d, J=8.4 Hz, 2ArH), 8.25 (d, J=8.4 Hz, 2ArH), 9.25 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 16.1, 20.5, 22.4, 42.7, 55.8, 62.4, 123.4, 127.8, 145.0, 147.3, 169.9, 174.0, 182.5; MS (ESI): m/z=387.1 $[M+Na]^+$, 751.2 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{20}N_4O_4S$: C, 52.73; H, 5.53; N, 15.37. Found: C, 52.69; H, 5.59; N, 15.30.

4.2.19. Compound 1s. White solid, mp 148–150 °C; IR (KBr) 3304, 2966, 1745, 1658, 1516, 1475, 1371, 1132, 681 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.4 Hz, 3H), 1.15 (d, J=7.2 Hz, 3H), 1.60–1.67 (m, 2H), 2.06 (s, 3H), 3.71 (t, J=7.4 Hz, 2H), 4.39 (q, J=7.2 Hz, 1H), 7.59 (d, J=8.7 Hz, 1H), 7.71 (t, J=7.8 Hz, 1ArH), 7.86 (d, J=7.5 Hz, 1ArH), 8.19 (s, 1ArH), 8.22 (d, J=8.1 Hz, 1ArH), 9.27 (d, J=7.2 Hz, 8.7H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 16.2, 20.5, 22.4, 42.7, 55.7, 62.1, 120.9, 123.2, 130.1, 133.1, 139.9, 147.9, 170.0, 173.93, 182.6; MS (ESI): m/z=387.1 $[M+Na]^+$, 751.3 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{20}N_4O_4S$: C, 52.73; H, 5.53; N, 15.37. Found: C, 52.78; H, 5.50; N, 15.35.

4.2.20. Compound 1t. White solid, mp 158–160 °C; IR (KBr) 3258, 2962, 2931, 1752, 1664, 1555, 1420, 1355, 1299, 1134 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.5 Hz, 3H), 1.13 (d, J=6.9 Hz, 3H), 1.61–1.63 (m, 2H), 2.02 (s, 3H), 3.68 (t, J=4.2 Hz, 2H), 4.32 (q, J=6.9 Hz, 1H), 7.38 (d, J=8.7 Hz, 2ArH), 7.45–7.50 (m, 2ArH, 1CH–Ar), 9.10 (d, J=9.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 16.2, 20.5, 22.4, 42.6, 55.6, 62.3, 128.2, 128.3, 132.7, 136.6, 169.9, 174.0, 182.4; MS (ESI): m/z=376.1 $[M+Na]^+$, 729.2 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{20}ClN_3O_2S$: C, 54.31; H, 5.70; N, 11.87. Found: C, 54.39; H, 5.75; N, 11.81.

4.2.21. Compound 1u. White solid, mp 142–144 °C; IR (KBr) 3282, 2969, 2935, 1743, 1666, 1514, 1437, 1249, 1131, 1029 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.4 Hz, 3H), 1.12 (d, J=6.9 Hz, 3H), 1.57–1.66 (m, 2H), 2.01 (s, 3H), 3.69 (t, J=7.2 Hz, 2H), 3.75 (s, 3H), 4.29 (q, J=6.9 Hz, 1H), 6.94 (d, J=8.4 Hz, 2ArH), 7.28 (d, J=8.4 Hz, 2ArH), 7.45 (d, J=8.4 Hz, 1H), 9.02 (d, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.02, 16.39, 20.51, 22.36, 42.54, 55.13, 55.56, 62.52, 113.68, 127.40, 129.27, 158.99, 169.75, 174.11, 182.14; MS (ESI): m/z=372.2 $[M+Na]^+$, 721.3 $[2M+Na]^+$. Anal. Calcd for $C_{17}H_{23}N_3O_3S$: C, 58.43; H, 6.63; N, 12.02. Found: C, 58.49; H, 6.60; N, 12.08.

4.3. General procedure for the synthesis of compounds 3

To a stirred solution of 3-propyl-2-thiohydantoin (2.4 mmol) and aromatic aldehydes (1 mmol) in CH_3CN (8 mL), $BF_3\cdot Et_2O$ (1.2 mmol) was added at −15 °C. The reaction mixture was stirred for 12 h at the same temperature. By adding a saturated $NaHCO_3$ aqueous solution, the reaction was quenched. The mixture was extracted with ethyl acetate (20 mL×2) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by column chromatography on silica gel (petroleum ether–EtOAc, 2:1) to give compound **3**.

4.3.1. Compound 3a. White solid, mp 206–208 °C; IR (KBr) 2961, 2937, 1750, 1462, 1403, 1338, 1212, 1124, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.5 Hz, 6H), 1.58–1.63 (m, 4H), 3.67 (t, J=7.4 Hz, 4H), 4.18 (dd, J=18.9 Hz, 4H), 7.33–7.45 (m, 5ArH), 7.97 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 20.4, 42.7, 50.2, 68.8, 127.3, 128.9, 129.0, 133.2, 170.7, 183.1; MS (ESI): m/z=427.2 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{24}N_4O_2S_2$: C, 56.41; H, 5.98; N, 13.85. Found: C, 56.49; H, 6.01; N, 13.79.

4.3.2. Compound 3b. White solid, mp 138–140 °C; IR (KBr) 2967, 2936, 1748, 1465, 1358, 1205, 1123, 651 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.4 Hz, 6H), 1.58–1.65 (m, 4H), 3.66 (t, J=7.2 Hz, 4H), 4.18 (dd, J=19.2 Hz, 4H), 7.40 (d, J=8.4 Hz, 2ArH), 7.49 (d, J=8.4 Hz, 2ArH), 7.93 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.4, 42.8, 50.2, 68.3, 129.0, 129.4, 132.3, 133.6, 170.7, 183.2; MS (ESI): m/z=461.0 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{23}ClN_4O_2S_2$: C, 51.98; H, 5.28; N, 12.76. Found: C, 51.91; H, 5.33; N, 12.71.

4.3.3. Compound 3c. White solid, mp 212–214 °C; IR (KBr) 2970, 2936, 1748, 1463, 1380, 1350, 1215, 1125, 690 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.87 (t, J=7.5 Hz, 6H), 1.56–1.65 (m, 4H), 3.66 (t, J=7.4 Hz, 4H), 4.19 (dd, J=19.2 Hz, 4H), 7.35–7.50 (m, 4ArH), 7.92 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.1, 20.4, 42.8, 50.3, 68.4, 126.2, 127.2, 129.1, 130.8, 133.9, 135.7, 170.7, 183.3; MS (ESI): m/z=461.0 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{23}ClN_4O_2S_2$: C, 51.98; H, 5.28; N, 12.76. Found: C, 52.01; H, 5.23; N, 12.81.

4.3.4. Compound 3d. White solid, mp 182–184 °C; IR (KBr) 2961, 2939, 1747, 1463, 1403, 1342, 1211, 1124, 659 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.2 Hz, 6H), 1.58–1.65 (m, 4H), 2.33 (s, 3H), 3.66 (t, J=7.2 Hz, 4H), 4.16 (dd, J=19.5 Hz, 4H), 7.23 (s, 4ArH), 7.90 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 20.4, 20.7, 42.7, 50.2, 68.8, 127.2, 129.6, 130.3, 138.4, 170.7, 183.0; MS (ESI): m/z=441.1 $[M+Na]^+$, 859.2 $[2M+Na]^+$. Anal. Calcd for $C_{20}H_{26}N_4O_2S_2$: C, 57.39; H, 6.26; N, 13.39. Found: C, 57.41; H, 6.30; N, 12.44.

4.3.5. Compound 3e. White solid, mp 179–181 °C; IR (KBr) 2960, 2935, 1751, 1465, 1403, 1359, 1210, 1123, 654 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.86 (t, J=7.4 Hz, 6H), 1.60–1.62 (m, 4H), 3.66 (t, J=7.1 Hz, 4H), 3.78 (s, 3H), 4.16 (dd, J=19.5 Hz, 4H), 6.97 (d, J=8.4 Hz, 2ArH), 7.27 (d, J=8.4 Hz, 2ArH), 7.84 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 11.0, 20.4, 42.6, 50.2, 55.2, 68.7, 114.3, 125.1, 128.8, 159.5, 170.7, 182.9; MS (ESI): m/z=457.0 $[M+Na]^+$, 891.1 $[2M+Na]^+$. Anal. Calcd for $C_{20}H_{26}N_4O_3S_2$: C, 55.28; H, 6.03; N, 12.89. Found: C, 55.34; H, 6.11; N, 12.93.

4.4. General procedure for the synthesis of compounds 4

To a stirred solution of 2-imidazolidinethione (1.2 mmol) and aromatic aldehydes (1 mmol) in CH_3CN or CH_3CH_2CN (8 mL), $TiCl_4$ (1.2 mmol) was added at −15 °C. The reaction mixture was stirred for 12 h at the same temperature. By adding a saturated $NaHCO_3$ aqueous solution, the reaction was quenched. The mixture was extracted with ethyl acetate (20 mL×2) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by column chromatography on silica gel (EtOAc) to give compound **4**.

4.4.1. Compound 4a. White solid, mp 161–162 °C; IR (KBr) 3301, 1624, 1541, 1512, 1478, 1428, 1276, 1243, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=1.96 (s, 3H), 3.18 (q, 1H), 3.47 (t, J=9.6 Hz, 3H), 3.62 (q, 1H), 7.27–7.41 (m, 5ArH, 1CH–Ar), 8.37 (s, 1H), 8.77 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 22.5, 40.1, 41.2, 43.4, 61.86, 126.2, 127.9, 128.5, 137.9, 169.0, 182.2; MS (ESI): m/z=272.4 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{15}N_3OS$: C, 57.81; H, 6.06; N, 16.85. Found: C, 57.84; H, 6.08; N, 16.80.

4.4.2. Compound 4b. White solid, mp 166–168 °C; IR (KBr) 3280, 1628, 1544, 1512, 1485, 1277, 1239, 1088, 1011 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=1.05 (t, J=7.6 Hz, 3H), 2.22–2.28 (m, 2H), 3.19 (q, 1H), 3.45 (t, J=9.2 Hz, 2H), 3.60 (q, 1H), 7.29 (d, J=8.4 Hz, 2ArH), 7.38 (d, J=8.4 Hz, 1H), 7.46 (d, J=8.4 Hz, 2ArH), 8.43 (s, 1H), 8.71 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 9.7, 28.1, 41.1, 43.3, 61.3, 128.0, 128.4, 132.4, 137.1, 172.5, 182.1; MS (ESI): m/z=320.5 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{16}ClN_3OS$: C, 52.43; H, 5.42; N, 14.11. Found: C, 52.49; H, 5.44; N, 14.14.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.002.

References and notes

1. (a) Dondoni, A.; Massi, A. *Acc. Chem. Res.* **2006**, *39*, 451; (b) Nari, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899; (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
2. (a) Muccioli, G. G.; Fazio, N.; Scriba, G. K. E.; Poppitz, W.; Cannata, F.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. *J. Med. Chem.* **2006**, *49*, 417; (b) Takahashi, A.; Matsuoka, H.; Yamada, K.; Uda, Y. *Food Chem. Toxicol.* **2005**, *43*, 521; (c) Kandra, L.; Remenyik, J.; Batta, G.; Somsák, L.; Gyémánt, G.; Park, K. H. *Carbohydr. Res.* **2005**, *340*, 1311; (d) Teng, X.; Degterev, A.; Jagtap, P.; Xing, X.; Choi, S.; Denu, R.; Yuan, J.; Cuny, G. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5039; (e) Szymańska, E.; Kieć-Kononowicz, K.; Białecka, A.; Kasprowicz, A. *Il Farmaco* **2002**, *57*, 39; (f) Gyémánt, G.; Kandra, L.; Nagy, V.; Somsák, L. *Biochem. Biophys. Res. Commun.* **2003**, *312*, 334; (g) Shih, R. U.; Wu, J.; Liu, Y.; Liang, Y. C.; Lin, S. Y.; Sheu, M. T.; Lee, W. S. *Biochem. Pharmacol.* **2004**, *67*, 67; (h) Tsuda, M.; Yasuda, T.; Fukushi, E.; Kawabata, J.; Sekiguchi, M.; Fromont, J.; Kobayashi, J. *Org. Lett.* **2006**, *8*, 4235.
3. (a) Chang, W. G.; Kulkarni, M. V.; Sun, C. M. *J. Comb. Chem.* **2006**, *8*, 141; (b) Fuentes, J.; Salameh, B. A. B.; Pradera, M. A.; Córdoba, F. J. F.; Gash, C. *Tetrahedron* **2006**, *62*, 97; (c) Beloglazkina, E. K.; Majouga, A. G.; Romashkina, R. B.; Zyk, N. B. V. *Tetrahedron Lett.* **2006**, *47*, 2957; (d) Nefzi, A.; Giulianotti, M.; Truong, L.; Rattan, S.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2002**, *4*, 175; (e) Lin, M. J.; Sun, C. M. *Tetrahedron Lett.* **2003**, *44*, 8739.
4. Roué, N.; Bergman, J. *Tetrahedron* **1999**, *55*, 14729.
5. Jakše, R.; Rečnik, S.; Golobič, A.; Golič, L.; Stanovnik, B. *Tetrahedron* **2001**, *57*, 8395.
6. Chérouvrier, J. R.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2002**, *43*, 8745.
7. Papeo, G.; Posteri, H.; Borghi, D.; Varasi, M. *Org. Lett.* **2005**, *7*, 5641.
8. (a) Khodair, A. I. *Carbohydr. Res.* **2001**, *331*, 445; (b) Davis, R. A.; Aaslbersber, W.; Meo, S.; Rocha, R. M. D.; Ireland, C. M. *Tetrahedron* **2002**, *58*, 3263; (c) Marton, J.; Enisz, J.; Hosztafi, S.; Tímár, T. *J. Agric. Food Chem.* **1993**, *41*, 148; (d) Kieć-Kononowicz, K.; Karolak-Wojciechowska, J.; Müller, C. E.; Schumacher, B.; Pękala, E.; Szymańska, E. *Eur. J. Med. Chem.* **2001**, *36*, 407; (e) Lindel, T.; Hoffmann, H. *Tetrahedron Lett.* **1997**, *38*, 8935.
9. (a) Park, K. H.; Kurth, M. J. *J. Org. Chem.* **1999**, *64*, 9297; (b) Sim, M. M.; Ganesan, A. *J. Org. Chem.* **1997**, *62*, 3230; (c) Severinsen, R.; Lau, J. F.; Bondensgaard, K.; Hansen, B. S.; Begtrup, M.; Ankersen, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 317; (d) Zhang, W.; Lu, Y. *Org. Lett.* **2003**, *5*, 2555; (e) Elokdah, H.; Sulkowski, T. S.; Abou-Gharbia, M.; Butera, J. A.; Chai, S. Y. *J. Med. Chem.* **2004**, *47*, 681.
10. Reyes, S.; Burgess, K. *J. Org. Chem.* **2006**, *71*, 2507.
11. Crystal structure of compound **1a** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 611294.
12. Crystal structure of compound **3d** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 619508.
13. Corma, A.; García, H. *Chem. Rev.* **2003**, *103*, 4307.
14. (a) Majetich, G.; Hicks, R.; Zhang, Y.; Tian, X.; Feltman, T. L.; Fang, J.; Duncan, S., Jr. *J. Org. Chem.* **1996**, *61*, 8169; (b) Bartoli, G.; Bosco, M.; Sambri, L. *Tetrahedron Lett.* **1997**, *38*, 3785; (c) Shimada, T.; Yoshioka, M.; Konno, T.; Ishihara, T. *Org. Lett.* **2006**, *8*, 1129; (d) Ferreira, M. J.; Martins, A. M. *Coord. Chem. Rev.* **2006**, *250*, 118.
15. (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045; (b) Top, S.; Jaouen, G. *J. Org. Chem.* **1981**, *46*, 78.
16. (a) Zhang, Q.; Sun, S.; Hu, J.; Liu, Q.; Tan, J. *J. Org. Chem.* **2007**, *72*, 139; (b) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 3rd ed.; Wiley Interscience: New York, NY, 1985; p 862.