Synthesis of Aromatic Carbonyl Thiourea PI-28 Derivatives for the Development of Radicle Elongation Inhibitor of Parasitic Weeds

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Abstract

Aromatic carbonyl thiourea PI-28 has been focused on as a lead compound for the developing radicle elongation inhibitors in germinating Orobanche minor dry seeds. In this study, we have synthesized PI-28 and its derivatives using commercially available phenols, 2-chloroacetamide, and aryl isothiocyanates. In this method, 2-aryloxyacetanilides, which are also attractive as bioactive compounds, were obtained as byproducts. These compounds were formed due to the loss of isothiocyanate moiety from the formed aromatic carbonyl thioureas.

Introduction

Carbonyl thiourea is an important functional group for biologically active molecules, such as pharmaceuticals and agrochemicals.[1] For examples, some carbonyl thioureas inhibit P2X receptors for the treatment of inflammation and neurological disorders,[2] anti-amoebic properties,[3] antibacterial and antifungal activities,[4] and insecticidal avtivity.[5] Recently, Okazawa reported that aromatic carbonyl thiourea PI-28 (Figure 1) exhibits interesting activity in the screening of chemical libraries to identify radicle elongation inhibitors in germinating *Orobanche minor* dry seeds.[6] Therefore, in this study, we focused on PI-28 as a lead compound for the development of inhibitors with higher activity. In previous synthesis methods of aromatic carbonyl thioureas, thiocyanates or their tautomeric isothiocyanates were conveniently used;[7] for example, the reactions of thiocyanic acid with an acid halide and a primary amine,[8] thiocyanic acid with carboxylic acid and a primary amine,[9] thiocyanate with an acid halide and a primary amine,[2,10] carbonyl isothiocyanate with a primary amine,[11] and isothiocyanate with a benzamide.[12] For the synthesis of aromatic carbonyl thioureas **3** (PI-28 derivatives), we selected a combination of aliphatic primary amides, 2-aryloxyacetamides **1**, and commercially available *N*-aryl isothiocyanates **2** because 2-aryloxyacetamides **1** can be easily to prepared by the Williamson ether synthesis using 2-chloroacetamide and phenols (Scheme 1).[13]

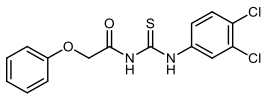
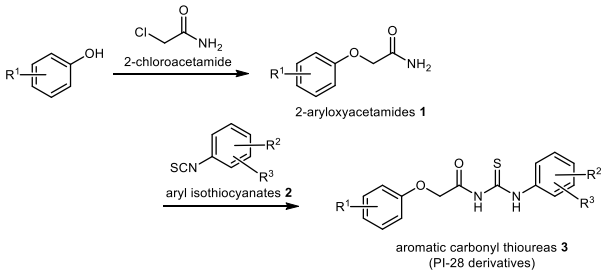


Figure 1. Chemical structure of PI-28



Scheme 1. Two-step synthesis of aromatic carbonyl thioureas **3** (PI-28 derivatives)

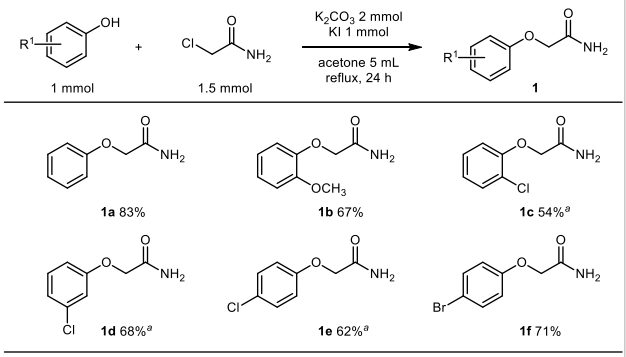
Herein, we report the synthesis of aromatic carbonyl thiourea PI-28 derivatives using phenols, 2-chloroacetamide, and aryl isothiocyanates **2** in a two-step reaction.

Results and Discussion

2-Phenoxyacetamide (**1a**) was synthesized by reaction of phenol (1 mmol) with 2-chloroacetamide (1.5 mmol) in acetone (5 mL) in the presence of potassium carbonate (2 mmol) and potassium iodide (1 mmol), following the reported reaction conditions.[13] The reaction proceeded efficiently to provide **1a** in 83% yield. Other 2-aryloxyacetamides were synthesized in a similar way, and their chemical structures are shown in Scheme 2. Yields of **1c**, **1d**, and **1e** were moderate because of their low solubility.

Next, we performed the reaction using 2-phenoxyacetamide (**1a**) and phenyl isothiocyanate (**2a**) by taking advantage of the condition for the reaction with a benzamide.[12] With the reaction between **1a** (0.5 mmol), **2a** (0.5 mmol), sodium hydride (0.5 mmol) as a base, and dry DMF (3 mL) as a solvent, the desired carbonyl thiourea **3a** was obtained in 39% yield. Moreover, 2-phenoxyacetanilide (**4a**) was unexpectedly obtained in 18% yield, losing an isothiocyanate moiety (entry 1 in Table 1). Although 2-aryloxyacetanilides **4** are also interesting compounds in the development of pharmaceuticals,[14] we optimized the reaction conditions to improve the yield of **3a**. A reaction temperature of 0 °C and a prolonged reaction time had no effect (entry 2). A higher reaction temperature of 80 °C resulted in the formation of **4a** in 80% yield as the sole product (entry 3). The use of THF as a solvent and triethylamine or potassium *tert*-butoxide as a base also had no effect (entries 4, 5, and 6). However, using **2a** (1.2 equiv.) and sodium hydride (1.2 equiv.) in dry DMF increased the yield of **3a** and **4a** to 60% and 40%, respectively (entry 7). The use of acetonitrile as the solvent resulted in decreased reactivity (entry 8). We were pleased to observe that the reaction proceeded smoothly with the use of DMSO as a solvent, and carbonyl thiourea **3a** was obtained in 76% yield (entry 9). The use of **1a** (1.2 equiv.) in DMSO provided **3a** in 66% yield, and **4a** was not detected (entry 10).

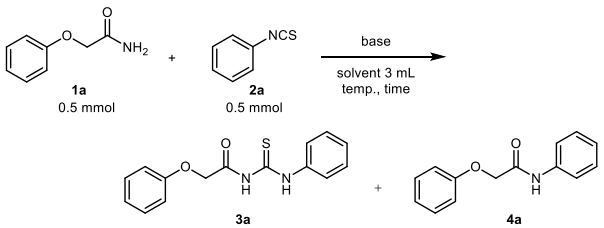
We examined the synthesis of the carbonyl thiourea PI-28 based on the results. The reaction of **1a** and 3,4-dichlorophenyl isothiocyanate (**2b**) was performed under



[a]ArOH (2 mmol), 2-chloroacetamide (3 mmol), K_2CO_3 (4 mmol), KI (2 mmol), and acetone (10 mL) were employed.

Scheme 2. Synthesis of various 2-aryloxyacetamides **1**

Table 1. Synthesis of aromatic carbonyl thiourea **3a**



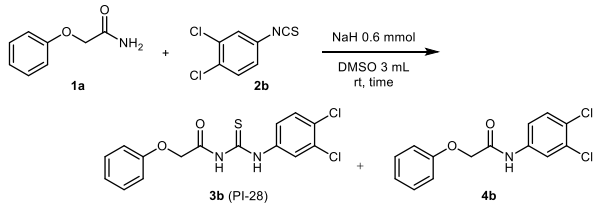
Entry	Base (eq.)		Solvent	Temp. (°C)	Time (h)	Yield (%) 3a	Yield (%) 4a
1	NaH	1	DMF	rt	3	39	18
2	NaH	1	DMF	0	18	14	14
3	NaH	1	DMF	80	5	0	80
4	NaH	1	THF	rt	3	25	4
5	Et_3N	2	THF	rt	24	N.D.[a]	N.D.[a]
6	^{t}BuOK	2	THF	50	24	trace	N.D.[a]
7[b]	NaH	1.2	DMF	rt	24	60	40
8[b]	NaH	1.2	CH_3CN	rt	2	20	5
9[b]	NaH	1.2	DMSO	rt	2	76	20
10[c]	NaH	1.2	DMSO	rt	2	66	N.D.[a]

[a]N.D.: not detected. [b]**2a** (0.6 mmol) was employed. [c]**1a** (0.6 mmol) was employed.

the reaction condition mentioned in entry 9 in Table 1. Contrary to our expectations, the reactivity was lowered, and 2-aryloxyacetanilide **4b** (29%) was obtained as a major product compared to the carbonyl thiourea **3b** (PI-28) (14%) (entry 1 in Table 2). When the reaction time was prolonged to 4 h, the yield of **4b** was increased to 40%, and that of desired **3b** was decreased to 4% (entry 2). These results suggest that the formed carbonyl thioureas **3** were converted to 2-aryloxyacetanilides **4** in the reaction system. It was found that **4b** was a major product, even when the reaction time was reduced to 1 h (entry 3). Then, the reaction was performed by reversing the amounts of the starting materials, that is, 1.2 equivalent of **1a** against **2b**; consequently, carbonyl thiourea **3b** was obtained as a major product in 40% yield (entry 4). The reaction time for 24 h decreased the yield of **3b** (4%) and increased that of **4b** (40%) (entry 5). Based on these results, the reaction conditions in entry 4 were used as the optimized conditions unless otherwise noted.

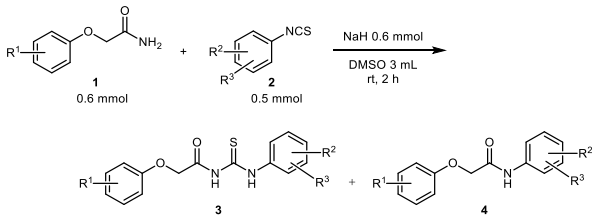
Next, the syntheses of aromatic carbonyl thiourea as the PI-28 derivatives were examined using aryloxyacetamides **1** and aryl isothiocyanates **2**, containing various substituents on each aromatic ring, and the results are summarized in Table 3. In all cases, the

Table 2. Synthesis of aromatic carbonyl thiourea **3b** (PI-28)



Entry	**1a**	**2b**	Time	Yield (%)	
	(mmol)	(mmol)	(h)	**3b**	**4b**
1	0.5	0.6	2	14	29
2	0.5	0.6	4	5	40
3	0.5	0.6	1	4	23
4	0.6	0.5	2	40	15
5	0.6	0.5	24	4	40

Table 3. Synthesis of various aromatic carbonyl thioureas **3** and 2-aryloxyacetanilides **4**



R^1	R^2	R^3	No.	Yield (%)	
				3	**4**
H	H	H	**a**[a]	76	20
H	3-Cl	4-Cl	**b**	40 (PI-28)	15
H	H	2-OCH_3	**c**[a]	96	N.D.[b]
H	H	2-F	**d**	89	trace
H	H	2-Cl	**e**	73	trace
H	H	3-CH_3	**f**[a]	88	N.D.[b]
H	H	3-F	**g**	54	12
H	H	3-CF_3	**h**	52	23
H	H	4-$N(CH_3)_2$	**i**	82	N.D.[b]
H	H	4-F	**j**	59	16
H	H	4-Cl	**k**	51	15
H	H	4-Br	**l**	63	7
H	H	4-OCF_3	**m**	60	25
H	H	4-CN	**n**	40	31
H	2-Cl	4-Cl	**o**	48	12
H	3-F	4-F	**p**	28	36
2-OCH_3	3-Cl	4-Cl	**q**	51	20
2-Cl	3-Cl	4-Cl	**r**	45	22
3-Cl	3-Cl	4-Cl	**s**	41	34
4-Cl	3-Cl	4-Cl	**t**	49	26
4-Br	3-Cl	4-Cl	**u**	27	22

[a]**1** (0.5 mmol) and **2** (0.6 mmol) were employed. [b]N.D.: not detected.

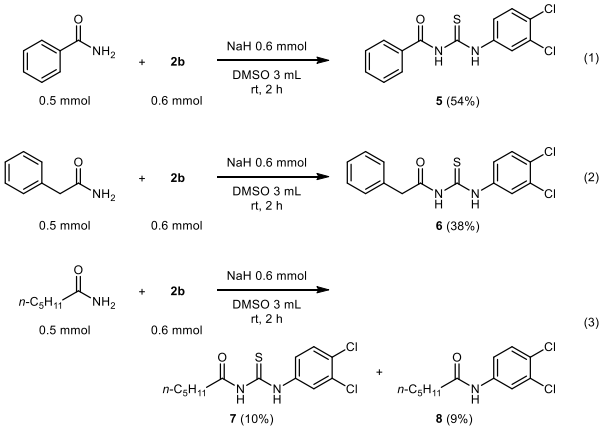
desired aromatic carbonyl thiourea **3** were obtained in moderate-to-good yields, although 2-aryloxyacetanilide **4** were also formed in many cases. The byproducts **4c**, **4f**, and **4i** were not detected when **2** containing the electron-donating methoxy, methyl, or *N*,*N*-dimethylamino group as a substrate were used. In the presence of a relatively strong electron-withdrawing group or two electron-

withdrawing halogen groups on the aromatic ring of **2**, not a small amount of **4** were obtained (**4m**-**4u**). The presence of a substituent on aromatic ring of **1** did not affect the formation of 2-aryloxyacetanilide (**4q**-**4u**).

For comparison, the results of the reactions using benzamide, 2-phenylacetamide, and hexanamide are shown in Scheme 3. When benzamide and 2-phenylacetamide were used as substrates, the corresponding aromatic carbonyl thioureas **5** and **6** were obtained in moderate yield, respectively. In both cases, the formation of the byproducts (acetanilides) were not detected at all. The reaction of hexanamide afforded the corresponding carbonyl thiourea **7** and anilide **8** although a significant decrease in reactivity was observed.

Conclusion

We have developed an efficient method for the synthesis of aromatic carbonyl thioureas (PI-28 derivatives) as candidates for radicle elongation inhibitors in germinating *Orobanche minor* dry seeds. The method involves a two-step reaction using commercially available phenols, 2-chloroacetamide, and aryl isothiocyanates. In most cases, 2-aryloxyacetanilides, which are also attractive bioactive compounds, were obtained simultaneously by the loss of the isothiocyanate moiety from aromatic carbonyl thioureas. At present, we are investigating the reaction mechanism for the formation of 2-aryloxyacetanilides and we are also evaluating the activity of PI-28 derivatives as radicle elongation inhibitors, and the results will be disclosed in due course.



Scheme 3. Reactions of amides with 3,4-dichlorophenyl isothiocyanate (**2b**)

Experimental Sections

General

IR spectra were recorded using samples prepared as liquid neat films on NaCl plate or KBr pellets with a JASCO FT/IR-460 Plus spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a JEOL JNM-ECZ500R spectrometer using $CDCl_3$ as a solvent at room temperature. Chemical shifts (δ) were determined in parts per million relative to tetramethylsilane (δ = 0.0 ppm) or $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR spectra and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectra. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Coupling constants (*J* value) are given in Hertz. High-resolution mass spectra (HRMS) were taken on a Bruker micrOTOF spectrometer by ESI methods. Melting points were determined by using a J-Science RFS-10 melting point apparatus. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. All reactions were monitored by thin-layer chromatography on silica gel plates (60 Å, F254), visualizing with ultraviolet light, unless otherwise stated. Column chromatography was performed on silica gel (Fuji Silysia Chemical , BW-200, 60−120 meshes) using hexanes and ethyl acetate as an eluent.

General procedure for the synthesis of aromatic carbonyl thioureas 3 and aryloxyacetanilides 4.

To a round bottom flask equipped with magnetic stir bar, 2-aryloxyacetamide **1** (0.6 mmol), DMSO (3 mL) and NaH (14.4 mg, 0.6 mmol) were added under an atmosphere of nitrogen. After the mixture was stirred at room temperature for 10 min, aryl isothiocyanate **2** (0.5 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h. The resulting reaction mixture

was then quenched with sat. NH_4Cl solution, and the aqueous phase was extracted with EtOAc (15 mL × 3). The organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the residue was purified by silica gel column chromatography with hexane/EtOAc as an eluent. The products 3 and 4 were isolated by GPC.

3-(2-Phenoxyacetyl)-1-phenylthiourea (3a)

3a was obtained as a white solid in 76% yield (109 mg); mp 107–109 °C; R_f = 0.33 (hexane/EtOAc = 3/1). IR (KBr): 3311, 3067, 2924, 1680, 1599, 1494, 1359, 1237, 1134, 754, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.12 (brs, 1H, NHC(O)), 9.41 (brs, 1H, NHC(S)), 7.68 (dd, J = 8.1, 1.2 Hz, 2H, Ar), 7.41 (ddd, J = 8.1, 8.1, 1.2 Hz, 2H, Ar), 7.36 (ddd, J = 8.1, 8.1, 1.2 Hz, 2H, Ar), 7.27 (t, J = 8.1 Hz, 1H, Ar), 7.08 (t, J = 8.1 Hz, 1H, Ar), 6.98 (dd, J = 8.1, 1.2 Hz, 2H, Ar), 4.60 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 168.6, 156.4, 137.5, 130.0, 128.9, 127.0, 124.1, 123.0, 115.0, 66.7. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{14}N_2NaO_2S$: 309.0668; found: 309.0655.

1-(3,4-Dichlorophenyl)-3-(2-phenoxyacetyl)thiourea (PI-28) (3b)

3b was obtained as a light brown in 40% yield (70 mg); mp 124–125 °C; R_f = 0.40 (hexane/EtOAc = 2/1). IR (KBr): 3383, 3038, 1699, 1604, 1514, 1356, 1239, 1151, 8145, 751, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.20 (brs, 1H, NHC(O)), 9.49 (brs, 1H, NHC(S)), 7.94 (d, J = 2.3 Hz, 1H, Ar), 7.54 (dd, J = 8.6, 2.3 Hz, 1H, Ar), 7.47 (d, J = 8.6 Hz, 1H, Ar), 7.37 (dd, J = 8.0, 7.5 Hz, 2H, Ar), 7.10 (t, J = 7.7 Hz, 1H, Ar), 6.99 (d, J = 8.0 Hz, 2H, Ar), 4.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.4, 168.9, 156.2, 136.7, 132.7, 130.52, 130.46, 130.0, 125.6, 123.3, 123.1, 114.8, 66.5. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{12}Cl_2N_2NaO_2S$: 376.9889; found: 376.9894.

1-(2-Methoxyphenyl)-3-(2-phenoxyacetyl)thiourea (3c)

3c was obtained as a white solid in 96% yield (152 mg); mp 99–100 °C; R_f = 0.59 (hexane/EtOAc = 2/1). IR (KBr): 3370, 3301, 3102, 3058, 1683, 1601, 1552, 1519, 1490, 1373, 1230, 1134, 747, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.49 (brs, 1H, NHC(O)), 9.38 (brs, 1H, NHC(S)), 8.74 (dd, J = 7.7, 1.6 Hz, 1H, Ar), 7.37 (dd, J = 8.3, 8.3 Hz, 1H, Ar), 7.23 (ddd, J = 7.7, 7.7, 1.6 Hz, 2H, Ar), 7.09 (t, J = 8.3 Hz, 1H, Ar), 7.02 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H, Ar), 6.99 (d, J = 8.3 Hz, 2H, Ar), 6.96 (d, J = 7.7 Hz, 2H, Ar), 4.62 (s, 2H, CH_2), 3.94 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 168.1, 156.4, 150.6, 130.0, 127.0, 122.9, 122.8, 120.2, 114.8, 110.5, 66.6, 56.0. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{16}N_2NaO_3S$: 339.0774; found: 339.0829.

1-(2-Fluorophenyl)-3-(2-phenoxyacetyl)thiourea (3d)

3d was obtained as a white solid in 89% yield (135 mg); mp 142–143 °C; R_f = 0.53 (hexane/EtOAc = 3/1). IR (KBr): 3367, 3058, 1692, 1597, 1489, 1363, 1142, 751, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.23 (brs, 1H, NHC(O)), 9.49 (brs, 1H, NHC(S)), 8.36 (ddd, J = 7.7, 7.7, 1.5 Hz, 1H, Ar), 7.37 (dd, J = 8.0, 7.5 Hz, 2H, Ar), 7.29–7.24 (m, 1H, Ar), 7.22–7.16 (m, 2H, Ar), 7.10 (t, J = 7.5 Hz, 1H, Ar), 6.99 (d, J = 8.0 Hz, 2H, Ar), 4.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 168.7, 156.4, 155.0 (d, $J_{C–F}$ = 248.7 Hz), 130.0, 127.8 (d, $J_{C–F}$ = 8.5 Hz), 125.9 (d, $J_{C–F}$ = 10.9 Hz), 125.4, 124.0 (d, $J_{C–F}$ = 3.6 Hz), 123.0, 115.6 (d, $J_{C–F}$ = 19.3 Hz), 115.0, 66.7. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{13}FN_2NaO_2S$: 327.0574; found 327.0564.

1-(2-Chlorophenyl)-3-(2-phenoxyacetyl)thiourea (3e)

3e was obtained as a white solid in 73% yield (118 mg); mp 115–116 °C; R_f = 0.52 (hexane/EtOAc = 2/1). IR (KBr): 3369, 3036, 1695, 1595, 1547, 1505, 1355, 1237, 1144, 751, 685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.30 (brs, 1H, NHC(O)), 9.50 (brs, 1H, NHC(S)), 8.37

(dd, J = 7.9, 1.5 Hz, 1H, Ar), 7.47 (dd, J = 7.9, 1.5 Hz, 1H, Ar), 7.38–7.32 (m, 3H, Ar), 7.23 (ddd, J = 7.9, 7.9, 1.5 Hz, 2H, Ar), 7.10 (t, J = 7.5 Hz, 1H, Ar), 6.99 (d, J = 8.0 Hz, 2H, Ar), 4.64 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.4, 168.9, 156.2, 136.7, 132.7, 130.52, 130.46, 130.0, 125.6, 123.3, 123.1, 114.8, 66.5. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{13}ClN_2NaO_2S$: 343.0278; cound 343.0278.

1-(3-Methylphenyl)-3-(2-phenoxyacetyl)thiourea (**3f**)

3f was obtained as a white solid in 88% yield (132 mg); mp 81–82 °C; R_f = 0.25 (hexane/EtOAc = 10/1). IR (KBr): 3390, 3052, 1694, 1572, 1491, 1360, 1220, 1140, 783, 751, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.08 (brs, 1H, NHC(O)), 9.42 (brs, 1H, NHC(S)), 7.50 (d, J = 8.0 Hz, 1H, Ar), 7.46 (s, 1H, Ar), 7.38–7.34 (m, 2H, Ar), 7.30 (t, J = 7.7, 1H, Ar), 7.10 (dd, J = 7.7, 7.7 Hz, 2H, Ar), 6.99 (d, J = 8.0 Hz, 2H, Ar), 4.61 (s, 2H, CH_2), 2.39 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 168.6, 156.3, 139.0, 137.3, 130.0, 128.7, 127.9, 124.6, 122.9, 121.2, 114.8, 66.5, 21.4. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{16}N_2NaO_2S$: 323.0825; found: 323.0832.

1-(3-Fluorophenyl)-3-(2-phenoxyacetyl)thiourea (**3g**)

3g was obtained as a pale yellow solid in 54% yield (83 mg); mp 107–109 °C; R_f= 0.75 (hexane/EtOAc = 2/1). IR (KBr): 3332, 3070, 1674, 1605, 1491, 1358, 1229, 1141, 1078, 863, 751, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.25 (brs, 1H, NHC(O)), 9.44 (brs, 1H, NHC(S)), 7.71 (d, J = 10.3 Hz, 1H, Ar), 7.39–7.35 (m, 4H, Ar), 7.10 (t, J = 7.5 Hz, 1H, Ar), 7.00–6.98 (m, 3H, Ar), 4.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1, 168.7, 162.5 (d, $J_{C–F}$ = 246.3 Hz), 156.3, 138.8 (d, $J_{C–F}$ = 10.9 Hz), 130.1, 130.0, 123.0, 119.4 (d, $J_{C–F}$ = 3.6 Hz), 114.8, 113.8 (d, $J_{C–F}$ = 21.7 Hz), 111.2 (d, $J_{C–F}$ = 25.4 Hz), 66.5. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{13}FN_2NaO_2S$: 327.0574; found 327.0565.

3-(2-Phenoxyacetyl)-1-(3-trifluoromethylphenyl)thiourea (**3h**)

3h was obtained as a light brown solid in 52% yield (92 mg); mp 101–103 °C; R_f= 0.11 (hexane/EtOAc = 10/1). IR (KBr): 3385, 3177, 3049, 2914, 1712, 1562, 1499, 1329, 1239, 1160, 1121, 749, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.29 (brs, 1H, NHC(O)), 9.47 (brs, 1H, NHC(S)), 8.00 (s, 1H, Ar), 7.92 (ddd, J = 4.3, 4.3, 1.7 Hz, 1H, Ar), 7.54–7.53 (m, 2H, Ar), 7.37 (dd, J = 8.0, 7.5 Hz, 2H, Ar), 7.10 (t, J = 8.0 Hz, 1H, Ar), 6.99 (dd, J = 8.0, 1.2 Hz, 2H, Ar), 4.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.5, 168.8, 156.2, 137.9, 131.3 (q, $J_{C–F}$ = 32.6 Hz), 130.0, 129.4, 127.2, 123.6 (q, $J_{C–F}$ = 272.8 Hz), 123.5 (d, $J_{C–F}$ = 3.6 Hz), 123.0, 120.8 (d, $J_{C–F}$ = 3.6 Hz), 114.8, 66.5. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{14}N_2NaO_2S$: 377.0542; found 377.0554.

1-(4-*N*,*N*-Dimethylaminophenyl)-3-(2-phenoxyacetyl)thiourea (**3i**)

3i was obtained as a yellow solid in 82% yield (136 mg); mp 144–145 °C; R_f = 0.53 (hexane/EtOAc = 3/1). IR (KBr): 3395, 3048, 2897, 1693, 1605, 1517, 1352, 1235, 1137, 817, 752, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.90 (brs, 1H, NHC(O)), 9.38 (brs, 1H, NHC(S)), 7.47–7.45 (AA'BB', 2H, Ar), 7.35 (dd, J = 8.4, 6.9 Hz, 2H, Ar), 7.08 (t, J = 6.9 Hz, 1H, Ar), 6.97 (d, J = 8.4 Hz, 2H, Ar), 6.73–6.70 (AA'BB', 2H, Ar), 4.57 (s, 2H, CH_2), 2.96 (s, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1, 168.5, 156.4, 149.4,129.9, 126.5, 125.3, 122.9, 114.9, 112.1, 66.6, 40.5. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{19}N_3NaO_2S$: 352.1090; found: 352.1062.

1-(4-Fluorophenyl)-3-(2-phenoxyacetyl)thiourea (**3j**)

3j was obtained as a yellow solid in 59% yield (90 mg); mp 123–125 °C; R_f = 0.38 (hexane/EtOAc = 3/1). IR (KBr): 3363, 3063, 1688, 1577, 1500, 1368, 1231, 1131, 825, 747, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.06 (brs, 1H, NHC(O)), 9.44 (brs, 1H, NHC(S)), 7.63–7.60 (AA'BB', 2H, Ar), 7.37 (ddd, J = 8.0, 8.0, 1.2 Hz, 2H,

Ar), 7.13–7.09 (m, 3H, Ar), 6.99 (dd, J = 8.0, 1.2 Hz, 2H, Ar), 4.62 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 168.7, 160.9 (d, J_{C-F} = 252.3 Hz), 156.3, 133.4, 130.0, 126.3 (d, J_{C-F} = 8.5 Hz), 123.0, 115.8 (d, J_{C-F} = 22.9 Hz), 114.8, 123.1, 66.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{13}FN_2NaO_2S$: 327.0574; found 327.0558.

1-(4-Chlorophenyl)-3-(2-phenoxyacetyl)thiourea (3k)

3k was obtained as an orange solid in 51% yield (81 mg); mp 131–132 °C; R_f = 0.50 (hexane/EtOAc = 3/1). IR (KBr): 3363, 3058, 1697, 1605, 1487, 1362, 1241, 1143, 1089, 828, 757, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.15 (brs, 1H, NHC(O)), 9.44 (brs, 1H, NHC(S)), 7.66–7.63 (AA'BB', 2H, Ar), 7.40–7.35 (m, 4H, Ar), 7.10 (tt, *J* = 8.5, 1.2 Hz, 1H, Ar), 6.99 (dd, *J* = 8.5, 1.2 Hz, 2H, Ar), 4.62 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.4, 168.8, 156.3, 135.9, 132.3, 130.0, 129.1, 125.3, 123.0, 114.8, 66.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{13}ClN_2NaO_2S$: 343.0278; found 343.0248.

1-(4-Bromophenyl)-3-(2-phenoxyacetyl)thiourea (3l)

3l was obtained as a light brown in 63% yield (115 mg); mp 131–133 °C; R_f = 0.18 (hexane/EtOAc = 10/1). IR (KBr): 3362, 3057, 1695, 1601, 1517, 1361, 1241, 1143, 1074, 825, 752, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.15 (brs, 1H, NHC(O)), 9.45 (brs, 1H, NHC(S)), 7.61–7.59 (AA'BB', 2H, Ar), 7.54–7.52 (AA'BB', 2H, Ar), 7.37 (dd, *J* = 8.0, 8.0 Hz, 2H, Ar), 7.37 (dd, *J* = 8.0, 8.0 Hz, 2H, Ar), 7.10 (t, *J* = 8.0 Hz, 1H, Ar), 6.99 (d, *J* = 8.0 Hz, 2H, Ar), 4.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 168.8, 156.3, 136.4, 132.0, 130.0, 125.6, 123.0, 120.2, 114.8, 66.6. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{13}BrN_2NaO_2S$: 386.9773; found 386.9771.

3-(2-phenoxyacetyl)-1-(4-trifluoromethoxyphenyl)thiourea (3m)

3m was obtained as a pale orange solid in 60% yield (111 mg); mp 112–113 °C; R_f = 0.47 (hexane/EtOAc = 3/1). IR (KBr): 3360, 3060, 1698, 1514, 1304, 1205, 1146, 843, 754, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.18 (brs, 1H, NHC(O)), 9.45 (brs, 1H, NHC(S)), 7.74–7.73 (AA'BB', 2H, Ar), 7.36 (dd, *J* = 7.6, 6.9 Hz, 2H, Ar), 7.26–7.24 (AA'BB', 2H, Ar), 7.09 (t, *J* = 6.0 Hz, 1H, Ar), 6.98 (d, *J* = 7.6 Hz, 2H, Ar), 4.61 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.5, 168.8, 156.3, 147.2, 135.9, 130.0, 125.4, 123.0, 121.4, 120.4 (q, J_{C-F} = 258.3 Hz), 114.9, 66.6. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{13}F_3N_2NaO_3S$: 393.0491; found 393.0480.

1-(4-Cyanophenyl)-3-(2-phenoxyacetyl)thiourea (3n)

3n was obtained as a pale yellow solid in 40% yield (63 mg); mp 155–157 °C; R_f = 0.24 (hexane/EtOAc = 3/1). IR (KBr): 3371, 3023, 2222, 1694, 1599, 1496, 1353, 1228, 1134, 834, 756, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.48 (brs, 1H, NHC(O)), 9.47 (brs, 1H, NHC(S)), 7.95 (d, *J* = 8.3 Hz, 2H, Ar), 7.69 (d, *J* = 8.3 Hz, 2H, Ar), 7.37 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 2H, Ar), 7.11 (t, *J* = 7.6 Hz, 2H, Ar), 6.99 (d, *J* = 7.6 Hz, 2H, Ar), 4.64 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.9, 168.9, 156.2, 141.3, 132.9, 130.0, 123.4, 123.1, 118.3, 114.8, 109.8, 66.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{13}N_3NaO_2S$: 334.0621; found 334.0617.

1-(2,4-Dichlorophenyl)-3-(2-phenoxyacetyl)thiourea (3o)

3o was obtained as a pale orange solid in 48% yield (86 mg); mp 114–116 °C; R_f = 0.53 (hexane/EtOAc = 3/1). IR (KBr): 3363, 3333, 3006, 1698, 1583, 1501, 1349, 1233, 1141, 813, 751, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.31 (brs, 1H, NHC(O)), 9.51 (brs, 1H, NHC(S)), 8.38 (d, *J* = 8.6 Hz, 1H, Ar), 7.47 (d, *J* = 2.3 Hz, 1H, Ar), 7.36 (dd, *J* = 8.0, 7.5 Hz, 2H, Ar), 7.30 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar), 7.09 (t, *J* = 7.5 Hz, 1H, Ar), 6.98 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar), 4.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.5, 168.5, 156.2, 133.5, 132.4, 130.0, 129.4, 128.4, 127.2, 126.7, 123.0, 114.8, 66.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{12}Cl_2N_2NaO_2S$: 376.9889; found 376.9877.

1-(3,4-Difluorophenyl)-3-(2-phenoxyacetyl)thiourea (3p)

3p was obtained as a pale yellow solid in 28% yield (45 mg); mp 137–139 °C; R_f = 0.37 (hexane/EtOAc = 3/1). IR (KBr): 3352, 3039, 3166, 1696, 1577, 1512, 1429, 1367, 1279, 1238, 1209, 1136, 819, 754, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.16 (brs, 1H, NHC(O)), 9.45 (brs, 1H, NHC(S)), 7.79 (ddd, J = 11.5, 7.2, 2.6 Hz, 1H, Ar), 7.37 (dd, J = 8.0, 7.5 Hz, 2H, Ar), 7.31–7.28 (m, 1H, Ar), 7.20 (dd, J = 18.3, 8.6 Hz, 1H, Ar), 7.10 (t, J = 7.5 Hz, 1H, Ar), 6.99 (d, J = 8.0 Hz, 2H, Ar), 4.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 168.9, 156.2, 149.8 (dd, $J_{C–F}$ = 248.7, 13.3 Hz), 148.7 (dd, $J_{C–F}$ = 249.9, 12.1 Hz), 133.7 (dd, $J_{C–F}$ = 6.0, 3.6 Hz), 130.0, 123.1, 120.2 (d, $J_{C–F}$ = 6.0, 3.6 Hz), 117.3, 114.8, 113.8 (d, $J_{C–F}$ = 21.7 Hz), 66.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{12}F_2N_2NaO_2S$: 345.0480; found 345.0455.

1-(3,4-Dichlorophenyl)-3-[2-(2-methoxyphenoxy)acetyl]thiourea (3q)

3q was obtained as a pale brown solid in 51% yield (99 mg); mp 112–113 °C; R_f = 0.50 (hexane/EtOAc = 2/1). IR (KBr): 3347, 3058, 2950, 1670, 1604, 1506, 1358, 1229, 1132, 1025, 850, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.28 (brs, 1H, NHC(O)), 10.47 (brs, 1H, NHC(S)), 7.94 (d, J = 2.9 Hz, 1H, Ar), 7.53 (dd, J = 8.9, 2.9 Hz, 1H, Ar), 7.45 (d, J = 8.9 Hz, 1H, Ar), 7.12 (ddd, J = 8.0, 8.0, 1.7 Hz, 2H, Ar), 7.02 (dd, J = 8.0, 1.7 Hz, 1H, Ar), 6.98–6.93 (m, 2H, Ar), 4.66 (s, 2H, CH_2), 4.00 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.1, 170.4, 150.3, 147.2, 136.9, 132.6, 130.4, 130.2, 125.6, 124.9, 123.3, 121.2, 118.5, 112.1, 71.2, 56.0. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{14}Cl_2N_2NaO_3S$: 406.9994; found 406.9959.

3-[2-(2-Chlorophenoxy)acetyl]-1-(3,4-dichlorophenyl)thiourea (3r)

3r was obtained as a pale yellow solid in 45% yield (88 mg).; mp 171–172 °C; R_f = 0.50 (hexane/EtOAc = 3/1). IR (KBr): 3453, 3363, 3048, 1703, 1602, 1548, 1477, 1360, 1285, 1247, 1134, 810, 744, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.16 (brs, 1H, NHC(O)), 9.78 (brs, 1H, NHC(S)), 7.95 (d, J = 2.3 Hz, 1H, Ar), 7.57 (dd, J = 8.8, 2.3 Hz, 1H, Ar), 7.47 (d, J = 8.8 Hz, 1H, Ar), 7.46 (dd, J = 8.0, 1.5 Hz, 1H, Ar), 7.29 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, Ar), 7.07 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, Ar), 6.95 (d, J = 8.0, 1.5 Hz, 1H, Ar), 4.67 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 168.1, 152.1, 136.8, 132.7, 130.8, 130.5, 130.4, 128.1, 125.5, 124.0, 123.7, 123.2, 114.7, 67.6. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{11}Cl_3N_2NaO_2S$: 410.9499; found 410.9459.

3-[2-(3-Chlorophenoxy)acetyl]-1-(3,4-dichlorophenyl)thiourea (3s)

3s was obtained as a light brown solid in 41% yield (80 mg); mp 125–126 °C; R_f = 0.53 (hexane/EtOAc = 3/1). IR (KBr): 3378, 3039, 1695, 1596, 1512, 1349, 1276, 1219, 1134, 1072, 851, 769, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.15 (brs, 1H, NHC(O)), 9.37 (brs, 1H, NHC(S)), 7.93 (d, J = 2.3 Hz, 1H, Ar), 7.53 (dd, J = 8.9, 2.3 Hz, 1H, Ar), 7.45 (d, J = 8.9 Hz, 1H, Ar), 7.28 (dd, J = 8.0, 8.0 Hz, Ar), 7.08 (ddd, J = 8.0, 2.6, 1.2 Hz, 1H, Ar), 6.99 (d, J = 1.2, 1.2 Hz, 1H, Ar), 6.88 (ddd, J = 8.0, 2.6, 1.2 Hz, 1H), 4.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 168.1, 156.7, 136.6, 135.4, 132.7, 130.8, 130.5, 130.4, 125.5, 123.3, 123.2, 115.4, 113.1, 66.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{11}Cl_3N_2NaO_2S$: 410.9499; found 410.9500.

3-[2-(4-Chlorophenoxy)acetyl]-1-(3,4-dichlorophenyl)thiourea (3t)

3t was obtained as a brown solid in 49% yield (95 mg); mp 128–129 °C; R_f = 0.50 (hexane/EtOAc = 3/1). IR (KBr): 3377, 3065, 1705, 1593, 1515, 1360, 1234, 1146, 814, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.16 (brs, 1H, NHC(O)), 9.38 (brs, 1H, NHC(S)), 7.94 (d, J = 2.6 Hz, 1H, Ar), 7.54 (dd, J = 8.6, 2.9 Hz, 1H, Ar), 7.47 (d, J

= 8.6 Hz, 1H, Ar), 7.35–7.31 (AA'BB', 2H, Ar), 6.94–6.91 (AA'BB', 2H, Ar), 4.60 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 168.3, 154.8, 136.7, 132.7, 130.5, 130.4, 129.9, 128.1, 125.5, 123.2, 116.2, 66.7. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{11}Cl_3N_2NaO_2S$: 410.9499; found 410.9471.

3-[2-(4-Bromophenoxy)acetyl]-1-(3,4-dichlorophenyl)thiourea (3u)

3u was obtained as a light brown solid in 27% yield (60 mg); mp 107–109 °C; R_f = 0.50 (hexane/EtOAc = 2/1). IR (KBr) 3342, 2982, 1691, 1585, 1478, 1352, 1233, 1129, 822, 695, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.16 (brs, 1H, NHC(O)), 9.37 (brs, 1H, NHC(S)), 7.94 (d, *J* = 2.3 Hz, 1H, Ar), 7.54 (dd, *J* = 8.9, 2.3 Hz, 1H, Ar), 7.49–7.46 (m, 3H, Ar), 6.89–6.86 (AA'BB', 2H, Ar), 4.60 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 168.2, 155.3, 136.6, 132.9, 132.8, 130.6, 130.5, 125.6, 123.2, 116.6, 115.6, 66.6. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{11}BrCl_2N_2NaO_2S$: 454.8994; found 454.8967.

3-Benzoyl-1-(3,4-dichlorophenyl)thiourea (5)[15]

5 was obtained as a white solid in 54% yield (88 mg); mp 148–149 °C; R_f = 0.53 (hexane/EtOAc = 3/1). ^1H NMR (500 MHz, $CDCl_3$): δ 12.69 (brs, 1H, NHC(O)), 9.14 (brs, 1H, NHC(S)), 7.99 (d, *J* = 2.6 Hz, 1H, Ar), 7.89 (dd, *J* = 7.5, 1.2 Hz, 2H, Ar), 7.67 (t, *J* = 7.5 Hz, 1H, Ar), 7.59–7.53 (m, 3H, Ar), 7.47 (d, *J* = 8.6 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 167.1, 136.9, 134.0, 132.7, 131.3, 130.4, 130.3, 129.3, 127.5, 125.6, 123.3.

1-(3,4-Dichlorophenyl)-3-(2-phenylacetyl)thiourea (6)

6 was obtained as a brown solid in 38% yield (62 mg); mp 118–119 °C; R_f = 0.47 (hexane/EtOAc = 3/1). IR (KBr): 3226, 3025, 1678, 1585, 1529, 1352, 1147, 8813, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.38 (brs, 1H, NHC(O)), 8.72 (brs, 1H, NHC(S)), 7.89 (d, *J* = 2.3 Hz, 1H, Ar), 7.48 (dd, *J* = 8.9, 2.3 Hz, 1H, Ar), 7.44–7.36 (m, 4H, Ar), 7.30 (dd, *J* = 7.7, 1.7 Hz, 2H, Ar), 3.73 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.1, 172.0, 136.7, 132.7, 131.7, 130.4, 129.5, 129.4 (2C), 128.4, 125.6, 123.2, 44.2. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{12}Cl_2N_2NaOS$: 360.9940; found 360.9964.

1-(3,4-Dichlorophenyl)-3-(*n*-hexanoyl)thiourea (7)

7 was obtained as a white solid in 9% yield (15 mg); mp 107–109 °C; R_f = 0.25 (hexane/EtOAc = 20/1). IR (KBr): 3235, 3027, 2959, 1689, 1598, 1532, 1467, 1330, 1164, 858, 802, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.48 (brs, 1H, NHC(O)), 8.88 (brs, 1H, NHC(S)), 7.92 (d, *J* = 2.3 Hz, 1H, Ar), 7.51 (dd, *J* = 9.2, 2.3 Hz, 1H, Ar), 7.46 (d, *J* = 9.2 Hz, 1H, Ar), 2.40 (t, *J* = 7.6 Hz, 2H, $CH_2C(O)$), 1.71 (tt, *J* = 7.6, 6.9 Hz, 2H, $CH_2CH_2C(O)$), 1.38–1.34 (m, 4H, CH_2CH_2), 0.93 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 174.4, 136.8, 132.7, 130.6, 130.4, 125.7, 123.7, 37.3, 31.1, 24.4, 22.3, 13.8. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{16}Cl_2N_2NaOS$: 341.0253; found 341.0225.

Supporting Information

Supporting information for this article is available.

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Conflict of Interest

The authors declare no conflict of interest.

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