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Notes

An Efficient Synthesis of *N*,*N*-Dialkyl-5-(chlorophenyl)-2-furancarbothioamides from 2-Furoic Acid

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Thioamides are an important compound class due to their pharmacological activities, such as anti-influenza virus, antitumor, and anthelmintic properties.[1] Many furan compounds substituted at the 2- and 5-positions occur in nature, and their hydrazide derivatives exhibit diverse activities including fungicidal and herbicidal properties.[2] Among these, [5-(3,4-dichlorophenyl)furan-2-yl](piperidin-1-yl)methanethione (DFPM), which contains a 2,5-disubstituted furan skeleton, downregulates abscisic acid (ABA)-dependent gene expression and also inhibits ABA signal transduction.[3] Recently DFPM was found to generate specific growth arrest in the roots of the Arabidopsis plant.[4]

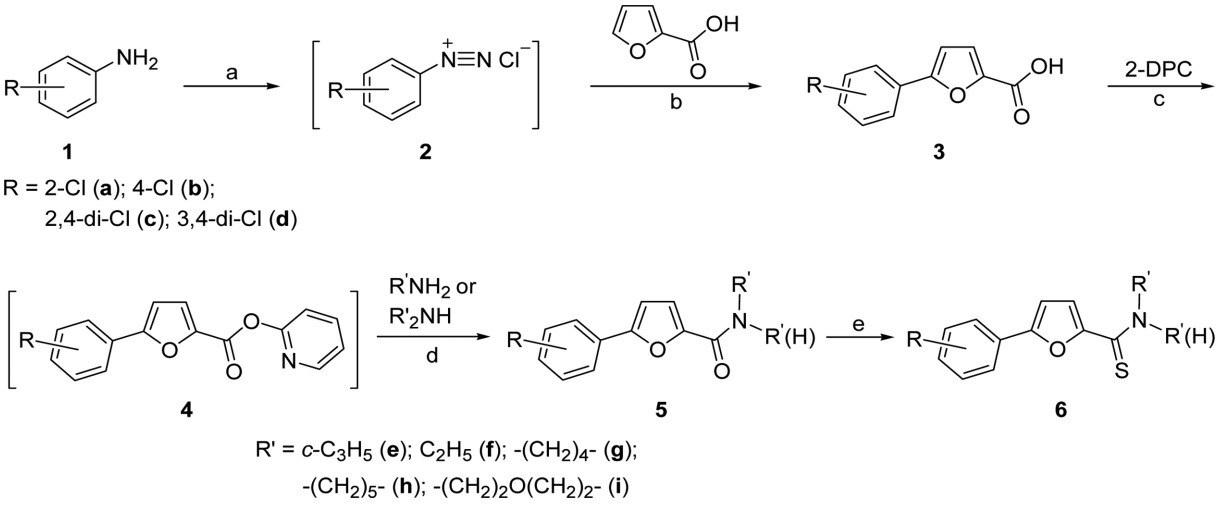
The synthesis of 5-(chlorophenyl)-2-furancarbothioamides consisted of preparation of 5-(chlorophenyl)-2-furoic acids, conversion to the amides, and subsequent thionation of the amides. 5-Phenyl-2-furoic acids have generally been prepared *via* oxidation of 5-phenyl-2-furaldehydes, which were obtained by Meerwein phenylation of 2-furancarboxaldehyde.[5] 5-Phenyl-2-furoic acids were also prepared by diazotization of 2-furoic acid using benzenediazonium salts[6] or by the cross-coupling reaction of 5-bromo-2-furoic acid with sodium tetraphenylborate in the presence of catalytic Pd/C under microwave irradiation or in open air.[7]

5-Phenyl-2-furancarboxamides have generally been synthesized by the acyl substitution of 5-phenyl-2-furoyl chlorides, derived from 5-phenyl-2-furoic acids and thionyl chloride, with amines.[8] The one-pot reaction of 5-phenyl-2-furoic acids and arylamines using phenylsulfonyl chloride also afforded *N*-aryl-5-phenyl-2-furancarboxamides.[9] Alternatively, the condensation of 5-bromo-2-furoic acid with arylamines using EDCl/HOBt afforded *N*-aryl-5-bromo-2-furancarboxamides. These amides were coupled with phenylboronic acid in the presence of $Pd(PPh_3)_4$ to give *N*-aryl-5-phenyl-2-furancarboxamides.[10] Conversion of 5-phenyl-2-furancarboxamides to their corresponding thioamides were typically carried out using 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide (Lawesson's reagent), which was widely used in the thionation of carbonyl groups.[11]

However, there have been no reports on the synthesis of 5-(chlorophenyl)-2-furancarbothioamides including DFPM. In this paper we describe an efficient synthesis of *N,N*-dialkyl-5-(chlorophenyl)-2-furancarbothioamides from 2-furoic acid under mild conditions as inhibitor candidates of plant growth.

5-(Chlorophenyl)-2-furoic acids (**3a**–**d**) were prepared by treating 2-furoic acid with chlorobenzenediazonium salts (**2a**–**d**). The addition of sodium nitrite to a solution of chloroanilines (**1a**–**d**) in aqueous HCl solution at 0 °C afforded the corresponding **2a**–**d** (*Scheme* 1). When 2-furoic acid and a catalytic amount of copper(II) chloride were added to **2**, highly regioselective electrophilic substitution occurred with phenylation at the 5-position of the furan ring. The reaction was complete in several hours, and **3a**–**d** were obtained in 56–65% yields after the usual work-up and recrystallization (**3a**: 57%, **3b**: 56%, **3c**: 62%, **3d**: 65%).

The synthesis of *N*,*N*-dialkyl-5-(chlorophenyl)-2-furancarboxamides (**5**) was carried out by the acyl substitution of 2-pyridyl 5-(chlorophenyl)-2-furoate intermediates **4** with amines. The addition of di-2-pyridyl carbonate (2-DPC)[12] to a solution of **3** in methylene chloride afforded the corresponding mixed carboxylic anhydrides, which was further converted to **4** with a catalytic amount of 4-(dimethylamino)pyridine (4-DMAP)[13] together with evolution of carbon dioxide. For instance, the reaction of 5-(3,4-dichlorophenyl)-2-furoic acid (**3d**) and 2-DPC in the presence of 0.1 equiv of 4-DMAP afforded 2-pyridyl 5-(3,4-dichlorophenyl)-2-furoate (**4d**) in 95% yield. The characteristic ^{1}H NMR values of pyridine ring were observed at δ 8.46 (dd, J = 4.9, 1.6 Hz, 1H), 7.82–7.89 (m, 1H), 7.24–7.31 (m, 2H)



***Scheme* 1.** Reagents and conditions: (a) 1.6 equiv $NaNO_2$, 18% *aq* HCl, H_2O, 0 °C, 20 min; (b) 0.3 equiv $CuCl_2$, acetone, 0 °C-rt, 5-6 h; (c) 0.1 equiv 4-DMAP, CH_2Cl_2, rt, 3 h; (d) 0 °C, 0.5 h; (e) 0.5 equiv (*p*-MeO-C_6H_4)$_2P_2S_4$, CH_2Cl_2, rt, 0.5-3.5 h; THF, 65 °C, 1.5 h for **6be**.

and the FT-IR carbonyl stretching peak was observed at 1739 cm^{-1} for **4d**. Typically, the synthesis of **5** was carried out in a one-pot process without isolation of **4**. Thus, amines were directly added to a solution of **4** in methylene chloride at 0 °C, and the reaction was complete in 0.5 h. After the usual basic work-up and chromatographic separation, **5** were obtained in 81–96% yields.

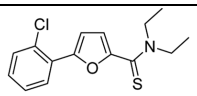
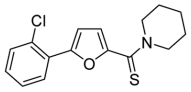
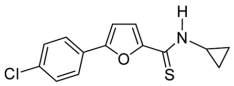
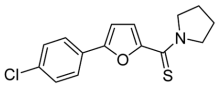
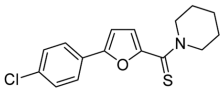
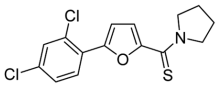
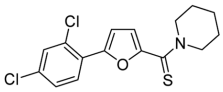
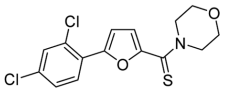
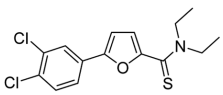
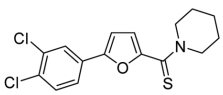
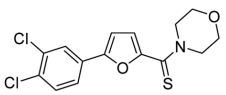
Conversion of **5** to *N*,*N*-dialkyl-5-(chlorophenyl)-2-furancarbothioamides (**6**) was carried out using Lawesson's reagent as an effective thionating agent of the carbonyl group. When Lawesson's reagent was added to a solution of **5** in methylene chloride, the sulfur atom of dithiophosphine ylide attacked the carbon atom of the carbonyl group in **5** to produce thiaoxaphosphetanes. These intermediates were cycloeliminated to give **6** together with metathiophosphonate (*p*-$MeOC_6H_4POS$).[14] The thionation of **5** using Lawesson's reagent was complete in 0.5–3.5 h at room temperature, and **6** were obtained in 87–96% yields after chromatographic separation. In the case of *N*-cyclopropyl-5-(4-chlorophenyl)-2-furancarboxamide (**5be**), thionation proceeded sluggishly in methylene chloride over 48 h at room temperature to give *N*-cyclopropyl-5-(4-chlorophenyl)-2-furancarbothioamide (**6be**) in 73% yield. However, the corresponding reaction of **5be** was complete in THF after 1.5 h at 65 °C to give **6be** in 90% yield.

As shown in *Table* 1, various *N*,*N*-dialkyl-5-(chlorophenyl)-2-furancarbothioamides were synthesized from 2-furoic acid in high overall yields (42–57%). Although thionation of secondary amide such as **5be** proceeded sluggishly, the conversion of other tertiary amides to the corresponding thioamides proceeded smoothly at room temperature. The condensation reaction of **3** with amines and thionation of **5** worked well under the present reaction conditions, regardless of the position of the chloro group in the 5-phenyl ring.

EXPERIMENTAL

Preparation of 5-(2,4-dichlorophenyl)-2-furoic acid (3c). To a suspension of 2,4-dichloroaniline (**1c**, 3.37 g, 20.8 mmol) in H_2O (10 mL), 18% HCl solution (8 mL) was added at 0 °C. After stirring for 20 min, a solution of sodium nitrite (1.44 g, 20.9 mmol) in H_2O (10 mL) was added, and the mixture was stirred further for 20 min. To the resulting solution of 2,4-dichlorobenzenediazonium chloride was added a solution of 2-furoic acid (1.46 g, 13.0 mmol) in acetone (7 mL), followed by the addition of a solution of copper(II) chloride (523 mg, 3.9 mmol) in H_2O (5 mL). The mixture was stirred for 6 h between 0 °C and room temperature. After evaporation of acetone, the mixture was poured into brine (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was washed with *n*-hexane and then recrystallized in 50% EtOAc/*n*-hexane to give **3c** (2.08 g, 62%) as a yellow solid. mp 223–225 °C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 13.58 (s, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.58 (dd, J = 8.6, 1.6 Hz, 1H), 7.33 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 159.3, 151.7, 145.3, 134.3, 131.3, 130.5, 129.9, 128.0, 127.0, 118.9, 113.1; Ms *m/z* (%) 256 (M^+,

***Table* 1.** Synthesis of *N,N*-dialkyl-5-(chlorophenyl)-2-furancarbo(thio)amides **5** and **6**

Entry	R	R'	Thioamides	Isolated yields, %[a]	
				5	**6**
af	2-Cl	C_2H_5		85	87 (42)
ah	2-Cl	-$(CH_2)_5$-		84	94 (45)
be	4-Cl	*c*-C_3H_5		94	90 (47)
bg	4-Cl	-$(CH_2)_4$-		81	92 (42)
bh	4-Cl	-$(CH_2)_5$-		93	94 (49)
cg	2,4-di-Cl	-$(CH_2)_4$-		89	94 (52)
ch	2,4-di-Cl	-$(CH_2)_5$-		88	94 (51)
ci	2,4-di-Cl	-$(CH_2)_2O(CH_2)_2$-		96	96 (57)
df	3,4-di-Cl	C_2H_5		81	91 (48)
dh	3,4-di-Cl	-$(CH_2)_5$-		93	92 (56)
di	3,4-di-Cl	-$(CH_2)_2O(CH_2)_2$-		89	96 (56)

[a]The numbers in parentheses indicate the overall yields of **6** from 2-furoic acid.

16), 214 (40), 212 (67), 183 (40), 151 (38), 149 (100).

Preparation of [5-(2,4-dichlorophenyl)furan-2-yl] (piperidin-1-yl)methanone (5ch). To a suspension of **3c** (771 mg, 3.0 mmol) in methylene chloride (18 mL), di-2-pyridyl carbonate (649 mg, 3.0 mmol) and 4-DMAP (37 mg, 0.3 mmol) was added at room temperature. After stirring for 3 h, the mixture was cooled to 0 ºC, and piperidine (326 μL, 3.3 mmol) was slowly added to the resulting 2-pyridyl 5-(2,4-dichlorophenyl)-2-furoate over 2 min. Stirring was continued for 0.5 h, and then the mixture was poured into saturated $NaHCO_3$ solution (40 mL) and extracted with methylene chloride (3 × 25 mL). The concentrated residue was purified by short pathway silica gel column chromatography using 50% EtOAc/*n*-hexane to give **5ch** (856 mg, 88%). mp 87–89 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 8.5, 2.0 Hz, 1H), 7.14 (d, J = 3.6 Hz, 1H), 7.02 (d, J = 3.6 Hz, 1H), 3.68–3.86 (m, 4H), 1.61–1.79 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 150.0, 147.6, 134.1, 131.3, 130.6, 129.0, 127.4, 127.1, 117.2, 112.2, 26.2, 24.7 (overlapped); Ms *m/z* (%) 327 (M^++4, 10), 325 (M^++2, 64), 323 (M^+, 100), 241 (69), 239 (95), 185 (56), 183 (92).

Preparation of [5-(2,4-dichlorophenyl)furan-2-yl] (piperidin-1-yl)methanethione (6ch). To a solution of **5ch** (778

mg, 2.4 mmol) in methylene chloride (12 mL), Lawesson's reagent (486 mg, 1.2 mmol) was added at room temperature, and the mixture was stirred for 5 h. After evaporation of methylene chloride, the residue was subjected to silica gel column chromatography using 30% EtOAc/*n*-hexane as eluant to give **6ch** (767 mg, 94%). The concentrated residue was further recrystallized in 10% EtOAc/*n*-hexane to give **6ch** as a yellow solid. mp 106–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.6 Hz, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.30 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.13 (d, *J* = 3.7 Hz, 1H), 7.11 (d, *J* = 3.7 Hz, 1H), 4.22–4.38 (m, 2H), 3.82–3.92 (m, 2H), 1.71–1.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.4, 151.8, 149.3, 134.1, 131.4, 130.7, 128.8, 127.5, 127.1, 118.9, 113.0, 54.1, 52.0, 27.1, 25.9, 24.3; Ms *m/z* (%) 343 (M^++4, 10), 341 (M^++2, 69), 339 (M^+, 100), 240 (63), 238 (96), 183 (30).

***N,N*-Diethyl-5-(2-chlorophenyl)-2-furancarbothioamide (6af):** mp 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.30–7.37 (m, 1H), 7.24–7.30 (m, 2H), 7.15 (d, *J* = 3.6 Hz, 1H), 3.93–4.19 (m, 2H), 3.82–3.93 (m, 2H), 1.30–1.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 152.0, 150.5, 131.0, 130.9, 128.9, 128.6, 128.1, 127.0, 120.2, 113.0, 48.1 (overlapped), 14.3, 11.2; Ms *m/z* (%) 295 (M^++2, 15), 293 (M^+, 38), 223 (40), 221 (100), 207 (44), 149 (30).

[5-(2-Chlorophenyl)furan-2-yl](piperidin-1-yl)methanethione (6ah): mp 78–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.29–7.34 (m, 1H), 7.21–7.27 (m, 1H), 7.15 (d, *J* = 3.6 Hz, 1H), 7.12 (d, *J* = 3.6 Hz, 1H), 4.18–4.34 (m, 2H), 3.90–4.05 (m, 2H), 1.73–1.84 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 151.7, 150.4, 130.9, 129.0, 128.6, 128.1, 127.0, 119.4 (overlapped), 112.8, 53.9, 52.0, 27.0, 26.0, 24.4; Ms *m/z* (%) 307 (M^++2, 39), 305 (M^+, 100), 223 (14), 221 (39), 204 (98), 149 (40).

***N*-Cyclopropyl-5-(4-chlorophenyl)-2-furancarbothioamide (6be):** mp 109–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 3.7 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 3.7 Hz, 1H), 3.31–3.40 (m, 1H), 1.01–1.08 (m, 2H), 0.79–0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.6, 153.9, 151.5, 134.7, 129.2, 128.0, 125.7, 119.8, 108.9, 28.1, 7.6; Ms *m/z* (%) 279 (M^++2, 12), 277 (M^+, 33), 264 (38), 262 (100), 223 (11), 221 (32), 149 (34).

[5-(4-Chlorophenyl)furan-2-yl](pyrrolidin-1-yl)methanethione (6bg): mp 142–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 3.6 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 3.6 Hz, 1H), 4.09–4.16 (m, 2H), 4.04–4.09 (m, 2H), 2.10–2.18 (m, 2H), 2.03–2.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 154.0, 152.3, 134.3, 129.2, 128.4, 125.5, 121.7, 107.9, 55.0, 53.6, 27.0, 23.8; Ms *m/z* (%) 293 (M^++2, 35), 291 (M^+, 100), 258 (42), 222 (61), 149 (46).

[5-(4-Chlorophenyl)furan-2-yl](piperidin-1-yl)methanethione (6bh): mp 111–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 3.6 Hz, 1H), 6.69 (d, *J* = 3.6 Hz, 1H), 4.10–4.38 (m, 2H), 3.82–4.10 (m, 2H), 1.75–1.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 152.9, 151.9, 134.1, 129.1, 128.5, 125.4, 120.0, 107.6, 53.7, 52.0, 27.2, 25.9, 24.4; Ms *m/z* (%) 307 (M^++2, 38), 305 (M^+, 100), 223 (15), 221 (39), 149 (32).

[5-(2,4-Dichlorophenyl)furan-2-yl](pyrrolidin-1-yl)methanethione (6cg): mp 172–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 3.7 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.15 (d, *J* = 3.7 Hz, 1H), 4.02–4.12 (m, 4H), 2.02–2.16 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 152.1, 150.5, 134.3, 131.6, 130.8, 128.8, 127.5, 127.1, 121.0, 113.3, 55.1, 53.7, 27.0, 23.8; Ms *m/z* (%) 329 (M^++4, 11), 327 (M^++2, 69), 325 (M^+, 100), 292 (43), 258 (41), 256 (59), 183 (30).

[5-(2,4-Dichlorophenyl)furan-2-yl](morpholino)methanethione (6ci): mp 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.31 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.19 (d, *J* = 3.7 Hz, 1H), 7.11 (d, *J* = 3.7 Hz, 1H), 4.05–4.35 (m, 4H), 3.80–3.93 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 151.3, 149.9, 134.4, 131.5, 130.7, 128.9, 127.6, 126.9, 120.3, 113.1, 66.7, 52.1; Ms *m/z* (%) 345 (M^++4, 10), 343 (M^++2, 61), 341 (M^+, 90), 259 (11), 257 (71), 255 (100), 183 (59).

***N,N*-Diethyl-5-(3,4-dichlorophenyl)-2-furancarbothioamide (6df):** viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 1.1 Hz, 1H), 7.45–7.49 (m, 2H), 7.24 (d, *J* = 3.6 Hz, 1H), 6.73 (d, *J* = 3.6 Hz, 1H), 4.03–4.13 (m, 2H), 3.72–3.82 (m, 2H), 1.35–1.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.9, 152.6, 151.6, 133.3, 132.1, 130.9, 129.9, 125.8, 123.2, 120.3, 108.6, 48.1 (overlapped), 14.3, 11.2; Ms *m/z* (%) 331 (M^++4, 4), 329 (M^++2, 25), 327 (M^+, 36), 259 (10), 257 (71), 255 (100), 183 (12).

[5-(3,4-Dichlorophenyl)furan-2-yl](piperidin-1-yl)methanethione (6dh): mp 111–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 1.0 Hz, 1H), 7.45–7.50 (m, 2H), 7.11 (d, *J* = 3.6 Hz, 1H), 6.72 (d, *J* = 3.6 Hz, 1H), 4.22–4.35 (m, 2H), 3.80–3.92 (m, 2H), 1.76–1.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 152.3, 151.5, 133.3, 132.1, 130.9, 129.9, 125.8, 123.2, 119.4, 108.5, 53.9, 52.5, 27.4, 26.1, 24.4; Ms *m/z* (%) 343 (M^++4, 11), 341 (M^++2, 69), 339 (M^+, 100), 242 (10), 240 (64), 238 (99), 183 (22).

[5-(3,4-Dichlorophenyl)furan-2-yl](morpholino)methanethione (6di): mp 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 1.1 Hz, 1H), 7.45–7.49 (m, 2H), 7.18 (d, J = 3.6 Hz, 1H), 6.73 (d, J = 3.6 Hz, 1H), 4.13–4.27 (m, 4H), 3.82–3.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 152.0, 151.7, 133.4, 132.4, 131.0, 129.6, 125.9, 123.3, 120.7, 108.6, 66.7, 51.3; Ms *m/z* (%) 345 (M^++4, 10), 343 (M^++2, 63), 341 (M^+, 92), 308 (51), 259 (12), 257 (72), 255 (100), 183 (42).

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