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Synthesis and biological activities of fluorine-containing *N*,*N*′-diphenylcarbamimidothioates

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Abstract

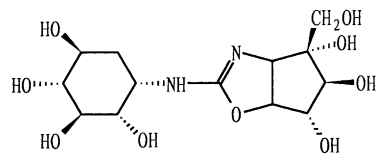
A series of fluorine-containing *N*,*N*′-diphenylcarbamimidothioates **6a-i** have been synthesized by treatment of the corresponding arylamine with the aryl isothiocyanate in ethanol at room temperature followed by treatment with methyl iodide. The antifungal activities against the fungi *Rhizoctonia solani* and *Pyricoraria orizae* of the title compounds have been screened.

Keywords: Synthesis; Biological activity; Fluorine-containing *N*,*N*′-diphenylcarbamimidothioates

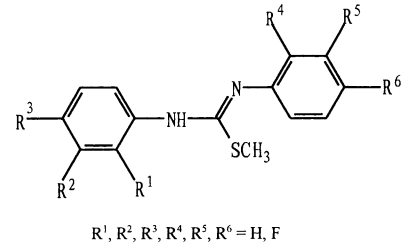
1. Introduction

Trehalase (EC 3.2.1.28), which specifically hydrolyses trehalose to two glucose moieties, is widely distributed in animals, plants, microorganisms and insects. The substrate trehalose is a main source of glucose in insects, yeast and fungi. In insects, trehalose is a principal blood sugar and is used to support various energy-requiring functions [1,2]. In yeast and fungi, trehalose is a major storage sugar and is responsible for the germination of ascospores [3,4]. Therefore, trehalase is a promising target for insecticides and fungicides.

Some trehalase inhibitors have been isolated from natural sources, such as deoxynojirimycin [5], salbostain [6], validamycins [7], validoxylamines [8] and the most potent one, trehazolin (**1**) [9]. It exhibits strong antifungal activity toward the plant pathogenic fungus, *Rhizoctonia solani* and *Pyricoraria orizae*. In the course of screening for novel trehalase inhibitors, we have designed a new group of compounds **6** based on the structural model of trehazolin.



(1)



R^1, R^2, R^3, R^4, R^5, R^6 = H, F

(6)

2. Results and discussion

The designed compounds were prepared by Scheme 1.

The aryl isothiocyanates (**3**) are commonly prepared from arylamines by treatment with carbon disulfide, aqueous ammonia and lead nitrate [10]. Other synthetic methods from monoarylthioureas [11] and phosphoramidates [12] have also been reported. However, most of these methods are

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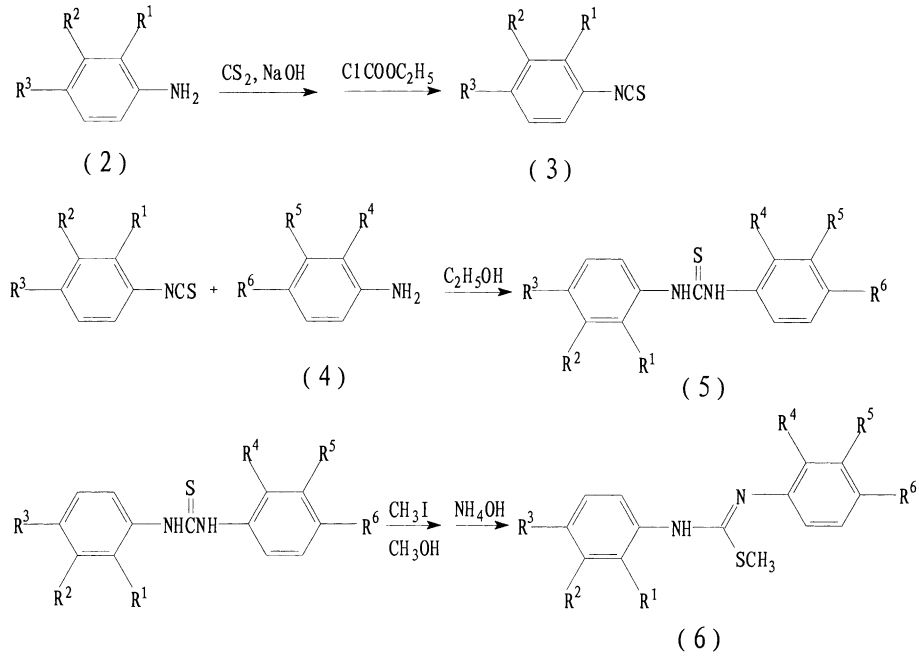

a) R^1 = F, R^2 = H, R^3 = H, R^4 = F, R^5 = H, R^6 = H b) R^1 = H, R^2 = H, R^3 = F, R^4 = H, R^5 = H, R^6 = F

c) R^1 = F, R^2 = H, R^3 = F, R^4 = F, R^5 = H, R^6 = F d) R^1 = F, R^2 = H, R^3 = F, R^4 = H, R^5 = F, R^6 = F

e) R^1 = F, R^2 = F, R^3 = F, R^4 = F, R^5 = H, R^6 = F f) R^1 = F, R^2 = F, R^3 = F, R^4 = H, R^5 = F, R^6 = F

g) R^1 = F, R^2 = F, R^3 = F, R^4 = F, R^5 = F, R^6 = F h) R^1 = H, R^2 = Cl, R^3 = F, R^4 = H, R^5 = Cl, R^6 = F

i) R^1 = F, R^2 = H, R^3 = Cl, R^4 = F, R^5 = H, R^6 = Cl

Scheme 1.

laborious and suffer from low yields. We designed a more straightforward and convenient route on the basis of the Kaluza reaction [13], by treatment of arylamines with carbon disulfide, sodium hydroxide and chloroformate [14].

The aryl isothiocyanates (**3**) were treated with fluorine-containing anilines in C_2H_5OH at room temperature to give the thioureas (**5**), which were treated with methyl iodide in CH_3OH followed by treatment with ammonia to give (**6**).

Compounds **6a-i** were screened for their antifungal activity against the fungi *R. solani* and *P. orizae* by the spore germination method [15] at 100 ppm concentration. The fungicidal data (Table 1) indicate that all of the compounds are highly toxic to the test fungi at 100 ppm concentration. The toxicity of the compound depends upon the number and position of the fluorines on the aryl rings. Introduction of chlorine on the aryl rings decreases the fungitoxicity of the compounds.

Table 1
Antifungal activity data of compounds **6a-i**

Compound	Antifungal activity at 100 ppm (%)	
	R. solani	*P. orizae*
6a	81.6	100
6b	78.9	100
6c	89.5	100
6d	84.2	100
6e	100	100
6f	77.6	100
6g	92.1	100
6h	38.3	92.3
6I	65.8	100

Because compounds **6a-i** were not soluble in water, their inhibitory activity toward trehalase in vitro cannot be determined by standard methods [9].

3. Experimental

Melting points were taken on a digital melting point apparatus made in Shanghai. Infrared spectra were measured on KBr disk using a Nicolet FT-IR-20SX instrument. Mass spectra were measured on a Hitachi M80 instrument. ^{1}H NMR spectra were obtained using a Brucker WP100SY (100 MHz) spectrometer with $(CD_3)_2CO$ as the solvent and TMS as internal standard. Combustion analyses for elemental composition were made with an Italian MOD.1106 analyzer. All reactions were monitored by TLC.

3.1. Preparation of aryl isothiocyanates (*3*)

The aryl isothiocyanates (**3**) were prepared according to our reported procedures [14] shown in Scheme 1. Yields and

boiling points are listed as follows.

- 2-Fluorophenyl isothiocyanate (**3a**): yield 68%, bp 103–104°C/8 Torr [14];
- 4-fluorophenyl isothiocyanate (**3b**): yield 72%, bp 95–97°C/8 Torr [14];
- 2,4-difluorophenyl isothiocyanate (**3c**): yield 89%, bp 85–86°C/8 Torr [14];
- 2,3,4-trifluorophenyl isothiocyanate (**3e**): yield 86%, bp 80–82°C/8 Torr [16];
- 3-chloro-4-fluorophenyl isothiocyanate (**3h**): yield 82%, bp 110–112°C/8 Torr [17];
- 2-fluoro-4-chlorophenyl isothiocyanate (**3i**): yield 85%, bp 108–109°C/8 Torr [14].

3.2. Preparation of *N,N′*-fluorosubstituted diphenylthioureas (**5**)

General procedure: to a solution of the fluorine-containing aniline **4** (0.01 mol) in 50 ml of ethanol was added dropwise, the aryl isothiocyanate **3** (0.01 mol) over a period of 10 min. Then the reaction mixture was stirred for 1 h at room temperature and left overnight. The solvent was removed under reduced pressure to give the crude product, which was recrystallized from ethanol to give a white solid. The following new compounds were prepared.

N,N′-Di(2-fluorophenyl)thiourea (**5a**): yield 92%, mp 154–155°C. IR (KBr) (cm^{-1}): 3140 (NH); 1350 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.84 (t, $J = 7.8$ Hz, 2H, H-6 and H-6′), 7.30 (m, 2H, H-4 and H-4′), 7.20 (t, $J = 8.6$ Hz, 4H, H-3, H-5, H-3′ and H-5′). Anal. Calc. for $C_{13}H_{10}F_2N_2S$ (264.29): C, 59.08; H, 3.81; N, 10.60%. Found: C, 59.21; H, 3.80; N, 10.62%.

N,N′-Di(4-fluorophenyl)thiourea (**5b**): yield 94%, mp 200–201°C. IR (KBr) (cm^{-1}): 3220 (NH); 1330 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.54 (dd, $J = 5.0$, 8.9 Hz, 4H, H-2, H-6, H-2′ and H-6′), 7.12 (t, 4H, $J = 8.9$ Hz, 4H, H-3, H-5, H-3′ and H-5′). Anal. Calc. for $C_{13}H_{10}F_2N_2S$ (264.29): C, 59.08; H, 3.81; N, 10.60%. Found: C, 59.25; H, 3.83; N, 10.58%.

N,N′-Di(2,4-difluorophenyl)thiourea (**5c**): yield 88%, mp 160–161°C. IR (KBr) (cm^{-1}): 3200 (NH); 1340 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.68 (td, $J = 6.2$, 9.0 Hz, 2H, H-6 and H-6′), 7.30 (t, $J = 9.1$ Hz, 2H, H-3 and H-3′), 7.05 (m, 2H, H-5 and H-5′). Anal. Calc. for $C_{13}H_8F_4N_2S$ (300.27): C, 52.00; H, 2.69; N, 9.33%. Found: C, 52.23; H, 2.67; N, 9.35%.

N-(2,4-difluorophenyl)-*N′*-(3,4-difluorophenyl)thiourea (**5d**): yield 90%, mp 137–138°C. IR (KBr) (cm^{-1}): 3200 (NH); 1350 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.78 (m, 1H, H-6′), 7.69 (td, $J = 6.1$, 8.8 Hz, 1H, H-6), 7.30 (m, 2H, H-2′, H-3), 7.11 (m, 1H, H-5′), 7.05 (m, 1H, H-5). Anal. Calc. for $C_{13}H_8F_4N_2S$ (300.27): C, 52.00; H, 2.69; N, 9.33%. Found: C, 52.18; H, 2.68; N, 9.28%.

N-(2,3,4-trifluorophenyl)-*N′*-(2,4-difluorophenyl)thiourea (**5e**): yield 87%, mp 144–145°C. IR (KBr) (cm^{-1}): 3240 (NH); 1350 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.70 (td, $J = 6.1$, 8.9 Hz, 1H, H-6′), 7.48 (m, 1H, H-6), 7.22 (td, $J = 2.3$, 8.9 Hz, 1H, H-5), 7.12 (m, 1H, H-5′), 7.05 (td, $J = 2.8$, 8.4 Hz, 1H, H-3′). Anal. Calc. for $C_{13}H_7F_5N_2S$ (318.19): C, 49.07; H, 2.22; N, 8.80%. Found: C, 49.21; H, 2.21; N, 8.78%.

N-(2,3,4-trifluorophenyl)-*N′*-(3,4-difluorophenyl)thiourea (**5f**): yield 86%, mp 155–156°C. IR (KBr) (cm^{-1}): 3200 (NH); 1350 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.77 (ddd, $J = 1.5$, 2.6, 7.4 Hz, 1H, H-6′), 7.48 (m, 1H, H-6), 7.33 (m, 2H, H-2′ and H-5), 7.21 (qd, $J = 1.2$, 9.4 Hz, 1H, H-5′). Anal. Calc. for $C_{13}H_7F_5N_2S$ (318.19): C, 49.07; H, 2.22; N, 8.80%. Found: C, 49.15; H, 2.20; N, 8.85%.

N,N′-Di(2,3,4-trifluorophenyl)thiourea (**5g**): yield 91%, mp 170–171°C. IR (KBr) (cm^{-1}): 3160 (NH); 1350 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.46 (m, 2H, H-6 and H-6′), 7.23 (td, $J = 2.3$, 9.4 Hz, 2H, H-5 and H-5′). Anal. Calc. for $C_{13}H_6F_6N_2S$ (336.25): C, 46.44; H, 1.80; N, 8.33%. Found: C, 46.30; H, 1.81; N, 8.35%.

N,N′-Di(3-chloro-4-fluorophenyl)thiourea (**5h**): yield 93%, mp 145–146°C. IR (KBr) (cm^{-1}): 3190 (NH); 1330 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.82 (dd, $J = 2.5$, 6.5 Hz, 2H, H-2 and H-2′), 7.49 (ddd, $J = 2$, 2.7, 4.2, 9.0 Hz, 2H, H-6 and H-6′), 7.30 (t, $J = 9.0$ Hz, 2H, H-5 and H-5′). Anal. Calc. for $C_{13}H_8Cl_2F_2N_2S$ (333.18): C, 46.86; H, 2.42; N, 8.41%. Found: C, 46.68; H, 2.41; N, 8.39%.

N,N′-Di(2-fluoro-4-chlorophenyl)thiourea (**5i**): yield 87%, mp 190–192°C. IR (KBr) (cm^{-1}): 3150 (NH); 1320 (C=S). ^{1}H NMR (CD_3COCD_3) δ: 7.84 (t, $J = 8.5$ Hz, 2H, H-6 and H-6′), 7.34 (dd, $J = 2.3$, 10.1 Hz, 2H, H-3 and H-3′), 7.27 (d, $J = 10.1$ Hz, 2H, H-5 and H-5′). Anal. Calc. for $C_{13}H_8Cl_2F_2N_2S$ (333.18): C, 46.86; H, 2.42; N, 8.41%. Found: C, 46.72; H, 2.40; N, 8.44%.

3.3. Preparation of fluorine-containing *N,N′*-diphenylcarbamimidothioates (**6**)

General procedure: to a solution of the thiourea **5** (0.005 mol) in 50 ml of methanol was added methyl iodide (0.85 g, 0.006 mol) and the mixture was heated to reflux for 6 h. Then the solvent was removed under reduced pressure, and the residue was added 50 ml of H_2O and 10 ml of concentrated aqueous ammonia. The precipitated product was filtered, washed with H_2O, and recrystallized from C_2H_5OH–H_2O (4:1) to give a white solid. The following new compounds were prepared.

Methyl *N,N′*-di(2-fluorophenyl)carbamimidothioates (**6a**): yield 72%, mp 70–71°C. IR (KBr) (cm^{-1}): 3210 (NH); 1590 (C=N). ^{1}H NMR (CD_3COCD_3) δ: 2.50 (s, 3H, –SCH_3), 6.85–7.95 (m, 8H, ArH). MS (EI, 70 eV) *m/z* (%): 278 (14) [M], 231 (38) [M–SCH_3], 230 (29) [M–CH_3SH], 168 (100) [M–C_6H_5FN], 153 (53) [M–C_6H_4FN–CH_4], 110 (38) [M–C_8H_7FNS], 95 (26) [M–$C_8H_8FN_2S$]. Anal. Calc. for $C_{14}H_{12}F_2N_2S$ (278.32): C, 60.42; H, 4.35; N, 10.07%. Found: C, 60.47; H, 4.37; N, 10.08%.

Methyl *N*,*N*′-di(4-fluorophenyl)carbamimidothioates (**6b**): yield 78%, mp 79–80°C. IR (KBr) (cm^{-1}): 3150 (NH); 1580 (C=N). ^1H NMR (CD_3COCD_3) δ: 2.42 (s, 3H, –SCH_3), 7.71 (m, 2H, H-2′ and H-6′), 7.05 (t, $J = 8.8$ Hz, 4H, H-3, H-5, H-3′ and H-5′), 6.90 (m, 2H, H-2 and H-6). MS (EI, 70 eV) *m*/*z* (%): 279 (47) [M + 1], 278 (63) [M], 231 (58) [M–SCH_3], 230 (82) [M–CH_3SH], 168 (100) [M–C_6H_5FN], 153 (48) [M–C_6H_4FN–CH_4], 110 (79) [M–C_8H_7FNS], 95 (62) [M–$C_8H_8FN_2S$]. Anal. Calc. for $C_{14}H_{12}F_2N_2S$ (278.32): C, 60.42; H, 4.35; N, 10.07%. Found: C, 60.54; H, 4.36; N, 10.05%.

Methyl *N*,*N*′-di(2,4-difluorophenyl)carbamimidothioates (**6c**): yield 83%, mp 79–80°C. IR (KBr) (cm^{-1}): 3210 (NH); 1560 (C=N). ^1H NMR (CD_3COCD_3) δ: 2.51 (s, 3H, –SCH_3), 6.88–7.92 (m, 6H, ArH). MS (EI, 70 eV) *m*/*z* (%): 314 (7) [M], 267 (17) [M–SCH_3], 266 (32) [M–CH_3SH], 186 (100) [M–$C_6H_4F_2N$], 171 (100) [M–$C_6H_3F_2N$–CH_4], 128 (62) [M–$C_8H_6F_2NS$]. Anal. Calc. for $C_{14}H_{10}F_4N_2S$ (314.30): C, 53.50; H, 3.21; N, 8.91%. Found: C, 53.46; H, 3.24; N, 8.87%.

Methyl *N*-(2,4-difluorophenyl)-*N*′-(3,4-difluorophenyl)-carbamimidothioates (**6d**): yield 87%, mp 78–79°C. IR (KBr) (cm^{-1}): 3160 (NH); 1580 (C=N). ^1H NMR (CD_3COCD_3) δ: 2.49 (s, 3H, –SCH_3), 7.91 (m, 1H, H-6′), 7.40 (m, 1H, H-2′), 7.30 (m, 1H, H-5′), 6.93–7.01 (m, 3H, H-3, H-5 and H-6). MS (EI, 70 eV) *m*/*z* (%): 314 (10) [M], 267 (78) [M–SCH_3], 266 (100) [M–CH_3SH], 186 (23) [M–$C_6H_4F_2N$], 171 (15) [M–$C_6H_3F_2N$–CH_4], 127 (35) [M–$C_8H_6F_2NS$], 95 (26) [M–$C_8H_7F_2N_2S$]. Anal. Calc. for $C_{14}H_{10}F_4N_2S$ (314.30): C, 53.50; H, 3.21; N, 8.91%. Found: C, 53.68; H, 3.22; N, 8.90%.

Methyl *N*-(2,3,4-trifluorophenyl)-*N*′-(2,4-difluorophenyl)carbamimidothioates (**6e**): yield 69%, mp 50–51°C. IR (KBr) (cm^{-1}): 3120 (NH); 1610 (C=N). ^1H NMR (CD_3COCD_3) δ: 2.50 (s, 3H, –SCH_3), 6.73–7.80 (m, 5H, ArH). MS (EI, 70 eV) *m*/*z* (%): 332 (33) [M], 285 (51) [M–SCH_3], 284 (100) [M–CH_3SH], 204 (100) [M–$C_6H_4F_2N$], 146 (23) [M–$C_8H_6F_2NS$], 145 (36) [M–$C_8H_7F_2NS$], 128 (28) [M–$C_8H_5F_3NS$], 127 (62) [M–$C_8H_6F_3NS$]. Anal. Calc. for $C_{14}H_9F_5N_2S$ (332.29): C, 50.60; H, 2.73; N, 8.43%. Found: C, 50.42; H, 2.71; N, 8.46%.

Methyl *N*-(2,3,4-trifluorophenyl)-*N*′-(3,4-difluorophenyl)carbamimidothioates (**6f**): yield 77%, mp 86–87°C. IR (KBr) (cm^{-1}): 3170 (NH); 1590 (C=N). ^1H NMR (CD_3COCD_3) δ: 2.50 (s, 3H, –SCH_3), 7.82 (m, 1H, H-6′), 7.41 (m, 1H, H-2′), 7.22 (q, 1H, $J = 9.3$ Hz, H-5′), 7.10 (m, 1H, H-5), 6.80 (m, 1H, H-6). MS (EI, 70 eV) *m*/*z* (%): 332 (8) [M], 285 (21) [M–SCH_3], 284 (100) [M–CH_3SH], 204 (16) [M–$C_6H_4F_2N$], 145 (13) [M–$C_8H_7F_2NS$], 127 (19) [M–$C_8H_6F_3NS$]. Anal. Calc. for $C_{14}H_9F_5N_2S$ (332.29): C, 50.60; H, 2.73; N, 8.43%. Found: C, 50.71; H, 2.72; N, 8.45%.

Methyl *N*,*N*′-di(2,3,4-trifluorophenyl)carbamimidothioates (**6g**): yield 81%, mp 65–66°C. IR (KBr) (cm^{-1}): 3160 (NH); 1570 (C=N). ^1H NMR (CD_3COCD_3) δ: 2.55 (s, 3H, –SCH_3), 7.51 (m, 1H, H-6′), 7.05–7.24 (m, 2H, H-5 and H-5′), 6.75 (m, 1H, H-6). MS (EI, 70 eV) *m*/*z* (%): 350 (10) [M], 303 (20) [M–SCH_3], 302 (39) [M–CH_3SH], 204 (100) [M–$C_6H_3F_3N$], 189 (44) [M–$C_6H_2F_3N$–CH_4], 146 (56) [M–$C_8H_5F_3NS$]. Anal. Calc. for $C_{14}H_8F_6N_2S$ (350.28): C, 48.01; H, 2.30; N, 8.00%. Found: C, 47.94; H, 2.32; N, 8.03%.

Methyl *N*,*N*′-di(3-chloro-4-fluorophenyl)carbamimidothioates (**6h**): yield 85%, mp 118–119°C. IR (KBr) (cm^{-1}): 3180 (NH); 1570 (C=N). ^1H NMR (CD_3COCD_3) δ: 2.43 (s, 3H, –SCH_3), 7.94 (m, 1H, H-2′), 7.58 (m, 1H, H-6′), 7.19 (t, $J = 9.0$ Hz, 2H, H-5 and H-5′), 7.01 (s, 1H, H-2), 6.85 (s, 1H, H-6). MS (EI, 70 eV) *m*/*z* (%): 346 (2) [M], 302 (12) [M–CH_3SH + 4], 300 (66) [M–CH_3SH + 2], 298 (100) [M–CH_3SH], 143 (15) [M–C_8H_6ClFNS], 129 (13) [M–$C_8H_7ClFN_2S$]. Anal. Calc. for $C_{14}H_{10}Cl_2F_2N_2S$ (347.21): C, 48.43; H, 2.90; N, 8.07%. Found: C, 48.62; H, 2.88; N, 8.09%.

Methyl *N*,*N*′-di(2-fluoro-4-chlorophenyl)carbamimidothioates (**6i**): yield 83%, mp 95–96°C. IR (KBr) (cm^{-1}): 3200 (NH); 1540 (C=N). ^1H NMR (CD_3COCD_3) δ: 2.50 (s, 3H, –SCH_3), 6.91–7.92 (m, 6H, ArH). MS (EI, 70 eV) *m*/*z* (%): 346 (6) [M], 302 (13) [M–CH_3SH + 4], 300 (67) [M–CH_3SH + 2], 298 (100) [M–CH_3SH], 204 (12) [M–C_6H_4ClFN + 2], 202 (35) [M–C_6H_4ClFN]. Anal. Calc. for $C_{14}H_{10}Cl_2F_2N_2S$ (347.21): C, 48.43; H, 2.90; N, 8.07%. Found: C, 48.58; H, 2.91; N, 8.10%.

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