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Synthesis and fungicidal activity of fluorine-containing phenylimino-thiazolidines derivatives

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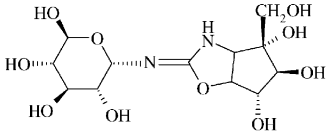
Abstract

Nine new fluorine-containing phenylimino-thiazolidines derivatives were prepared. The structures of all compounds were confirmed by ^{1}H NMR, mass and high resolution mass spectroscopy. The antifungicidal activities of the title compounds on *Phytophthora capsici* L., *Pyricularia oryzae* C, *Fusarium* spp. at 100 ppm were screened.

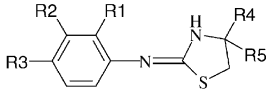
Keywords: Phenylimino-thiazolidines; Synthesis; Antifungicidal activity

1. Introduction

Recently, a variety of the reports regarding synthetic studies of the trehazolin derivatives have been presented due to the chemical and biological interests to the trehazolins [1–5]. Trehazolin, just like Validamycin A which has been commercialized and is used to control blight sheath of rice caused by the plant pathogenic fungus *Rhizoctonia solani*, is a slow, tight-binding inhibitor of trehalase [2,6]. It also shows potential fungicidal activity to control *Rhizoctonia solani* at 100 ppm [7]. But, the total synthesis of trehazolin is not an easily case, Shiozaki reported trehezolin was obtained from a 15-step synthesis starting from D-glucose, which was a convergent strategy [8–12]. It is difficult to make trehezolin if it is commercialized, thus, to modify and simplify trehezolin's structure and find commercialized compound is our interest. It is well known that many fluorine-containing compounds exhibit significant agricultural bioactivities owing to fluorine atom's unique properties, such as high thermal stability and lipophilicity [13]. Previously, we have reported fluorine-containing *N*,*N*′-diphenylcarbaminidothioates which exhibited fungicidal activity toward *Rhizoctonia solani* and *Pyricoraria oryzae* [14]. In this report, based on the structure features of trehazolin, we designed and synthesized fluorine-containing phenylimino-thiazolidines derivatives and investigated their bioactivities.



Trehazolin



By a facile and convenient method, novel fluorine-containing phenylimino-thiazolidines (**3a–i**) were synthesized. Very interestingly, the preliminary bioassay tests showed that some compounds (**3f**, **3g**) exhibited good fungiticidal activity on *Phytophthora capsici* L., *Pyricularia oryzae* C, *Fusarium* spp. at 100 ppm.

2. Results and discussion

The designed compounds were prepared by Fig. 1. The aryl isothiocyanates were commonly prepared from arylamines by treatment with carbon disulfide, aqueous sodium hydroxide and chloroformate according to our reported procedure [15].

Reaction of arylamines and carbon disulfide in NaOH solution was carried out to give intermediate dithiocarbamates. After adding ethyl chloroformate, aryl isothiocyanates

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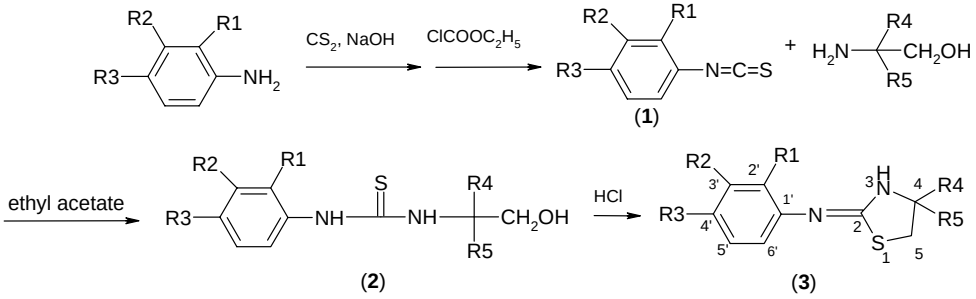

Fig. 1.

(**1**) was obtained. Compounds (**2**) was synthesized by reaction of aryl isothiocyanates (**1**) with substituted aminoethanol in ethyl acetate under reflux or at room temperature, the reaction rate depended on the nature of corresponding amine. When the substituents were –H, $–CH_3$, the corresponding compounds (**3**) could be synthesized easily at room temperature for a few minutes or half an hour, respectively. When the substituents were $–CH_2OH$ or $–CH_2CH_3$, the products could be obtained under reflux for 5–6 h. The target compounds (**3**) were obtained by heating of the compounds (**2**) in hydrochloric acid at 90 °C. It is shown in Fig. 1.

Compound no.	R1	R2	R3	R4	R5
3a	H	F	F	CH_3	CH_3
3b	H	F	F	CH_2OH	CH_2OH
3c	H	F	F	CH_2OH	CH_2CH_3
3d	H	H	F	CH_3	CH_3
3e	H	H	F	CH_2OH	CH_2CH_3
3f	H	H	F	H	H
3g	F	F	F	H	H
3h	F	F	F	CH_2OH	CH_2CH_3
3i	F	F	F	CH_3	CH_3

The fungicide activities of compound **3a–i** were screened at the concentration of 100 ppm according to the same method as literature [16]. The fungicidal data are listed in Table 1.

The data indicated compound **3g** and **3f** had good fungicidal activities among compounds **3a–i**. Even though the fungicidal activity of **3f** and **3g** to *Rhizoctonia solani* was not as high as trehazolin [2] and the series of *N*,*N*′-diphenylcarbamimidothioates [14], to our surprising, the compounds (**3f** and **3g**), especially **3f**, were highly toxic to *Phytophthora capsici* L., *Fusarium* spp., otherwise the series of *N*,*N*′-diphenylcarbamimidothioates or trehazolin had no antifungal activity to them. From the relationship between the structure of compounds **3a–i** and their bioactivity, it was found that the hydrophilicity of the substitution on five-membered heterocycle was important. In our previous study, we have synthesized non-fluorinated derivative, such as 2-(4-methylphenylimino)-tetrahydro-thiazolidine, 2-phenylimino-tetrahydro-thiazolidine and 2-(2-fluorophenylimino)-tetrahydro-thiazolidine [17]. These compounds also had no fungicidal activity to the fungi above. Thus, it was presumed that their fungicidal activities depended upon the position of the fluorine on the aryl rings and the substituent on five-membered heterocycle. When introducing hydrophilicity group on five-membered heterocycle, together with introducing the fluorine atom into the aryl rings, the bioactivity could increase. To the compounds with hydrogen atoms as the substituents R^4 and R^5 on five-membered heterocycles, when we introducing fluorine atom on *para* position or 1,2,3-positions, they showed significant biological activity, e.g. compound **3f** and **3g**. But, their antifungicidal activities decreased very quickly with the decrease of concentration, the further research on the modification of structure is in proceeding.

3. Experimental

Melting points were obtained with an electrothermal digital apparatus made in Beijing and are uncorrected. The infrared (IR) spectra were recorded on a Nicolet 470 infrared Fourier transform spectrometer using a potassium bromide pellets. The proton nuclear magnetic resonance (^{1}H NMR, 500 MHz) spectra were recorded on a Bruker WP-500SY spectrometers with CD_3COCD_3 as the solvent and TMS as an internal standard. High resolution mass spectra were obtained on MicroMass GCT CA 055 spectrometers. Analytical thin-layer chromatography (TLC) was carried out on precoated plate (silica gel 60 F_{254}), and spots were visualized with ultraviolet light. All chemicals or reagents were purchased from standard commercial suppliers.

3.1. Synthesis of phenylisothiocyanate (*1*)

To a stirred solution of sodium hydroxide (2.40 g, 0.06 mol) in 30 ml H_2O, carbon disulfide (4.57 g, 0.06 mol) was added at 2–5 °C, then, substituted aniline (0.06 mol) was added over a period of 30 min. After the mixture was refluxed for 24 h, ethyl chloroformate (6.51 g, 0.06 mol) was added dropwise at 35–40 °C and the resulting mixture was stirred for about 40 min at the same temperature. The organic phase was separated and washed with water, dried over anhydrous magnesium sulfate and concentrated

Table 1
Antifungal activity of $\mathbf{1}_{3a-i}$ at 100 ppm (%)

Compound	*Phytophthora capsici* L.	*Pyricularia oryzae* C.	*Fusarium* spp.	*Rhizoctonia Solani* K.
3a	5.1	1.8	2.3	9.8
3b	3.0	6.7	0.7	2.0
3c	50.0	57.0	1.0	0.7
3d	4.4	4.3	2.1	5.3
3e	8.2	1.3	3.7	4.6
3f	100	87.5	100	60.0
	42.9 (50 ppm)	25.0 (50 ppm)	33.3 (50 ppm)	–
3g	79.2	85.7	57.9	80.0
	21.4 (50 ppm)	12.5 (50 ppm)	22.2 (50 ppm)	–
3h	6.0	3.3	2.5	1.6
3i	2.2	1.3	8.9	11.3

under reduced pressure and the residue was distilled to obtain colorless liquid.

3.2. Synthetic procedure for substituted thiourea (*2*)

Appropriate amine was dissolved in ethyl acetate, and appropriate isothiocyanate was added dropwise with stirring and the mixture was kept at room temperature for 30–60 min or refluxed for 2–8 h. Then, the solvent was evaporated under reduced pressure to give the crude product, it could be used for the next reaction directly.

3.3. General synthetic procedure for substituted phenylimino-thiazolidine (*3*)

Appropriate thiourea (10 mmol) was dissolved in concentrated HCl (10 ml) and heated at 90 °C for 45 min. The cooled mixture was basified with 10 N NaOH in an ice bath. The solid was filtered and recrystallized or the precipitated gummy residue was extracted with Et_2O. The extract was washed with brine, dried and evaporated to dryness.

3.3.1. 2-(3,4-Difluorophenylimino)-4,4-dimethyl-thiazolidine (*3a*)

2-(3,4-Difluorophenylimino)-4,4-dimethyl-thiazolidine (**3a**) yield 68%, mp 183–184 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 1.40 (s, 6H, CH_3), 3.16 (s, 2H, H-5), 7.00 (br s, 1H, H-2′ and H-6′), 7.18 (q, 1H, $J_{3'5'} = 9.0$ Hz, $J_{5'6'} = 9.0$ Hz, $J_{4'5'} = 9.1$ Hz, H-5′). IR (KBr) (cm^{-1}): 3125 (NH), 2920, 2875 (C–H), 1630 (C=N), 1600, 1500 (Ph), 1280 (C–S), 1140, 870, 820, 780, 650. MS (EI, 70 eV): *m/z* (%): 242 (44.38) [*M*], 227 (100.00) [*M*–CH_3], 154 (22.18) [*M*–C_4H_8S], 129 (8.89), 88 (15.40), 55 (15.00). HRMS calculated for $C_{11}H_{12}F_2N_2S$: 242.0689; found: 242.0701.

3.3.2. 2-(3,4-Difluorophenylimino)-4,4-dihydroxymethyl-thiazolidine (*3b*)

2-(3,4-Difluorophenylimino)-4,4-dihydroxymethyl-thiazolidine (**3b**) yield 73%, mp 207–208 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 3.32 (s, 2H, H-5), 3.66 (d, 2H, $J = 11.0$ Hz, $CH_{2a(b)}OH$), 3.69 (d, 2H, $J = 11.0$ Hz, $CH_{2b(a)}OH$), 7.18 (q, 1H, $J_{3'5'} = 9.1$ Hz, $J_{4'5'} = 10.5$ Hz, $J_{5'6'} = 9.1$ Hz, H-5′), H-2′ and H-6′ (no signal). IR (KBr) (cm^{-1}): 3300 (OH), 3125 (NH), 2875, 1630 (C=N), 1600, 1510, 1200, 1050, 780. MS (EI, 70 eV): *m/z* (%): 274 (11.02) [*M*], 243 (100.00) [*M*–CH_2OH], 213 (56.94) [*M*–$C_2H_5O_2$], 155 (9.50), 128 (6.64), 113 (5.72), 88 (5.60). HRMS calculated for $C_{11}H_{12}F_2N_2O_2S$: 274.0588; found: 274.0585.

3.3.3. 2-(3,4-Difluorophenylimino)-4-ethyl-4-hydroxymethyl-thiazolidine (*3c*)

2-(3,4-Difluorophenylimino)-4-ethyl-4-hydroxymethyl-thiazolidine (**3c**) yield 51%, mp 143–144 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 1.00 (t, 3H, $J = 7.5$ Hz, CH_3), 1.76 (m, 2H, CH_2), 3.10 (d, 1H, $J = 10.9$ Hz, $H_{a(b)}$-5), 3.40 (d, 1H, $J = 10.9$ Hz, $H_{b(a)}$-5), 3.57 (d, 1H, $J = 10.9$ Hz, $H_{a(b)}$–CH_2OH), 3.61 (d, 1H, $J = 10.9$ Hz, $H_{b(a)}$–CH_2OH), 7.10 (br s, 1H, H-2′), 7.19 (q, 1H, $J_{4'5'} = J_{6'5'} = 9.0$ Hz, $J_{5'3'} = 9.0$ Hz, H-5′), 7.60 (br s, 1H, H-6′). IR (KBr) (cm^{-1}): 3300, 3100, 2875, 1640 (C=N), 1600, 1500 (Ph), 1280 (C–S), 1140, 870, 820, 780, 650. MS (EI, 70 eV) *m/z* (%): 272 (614) [*M*], 243 (6.12) [*M*–C_2H_5], 242 (11.41) [*M*–HCHO], 241 (100.00) [*M*–CH_2OH], 102 (30.04), 102 (9.56), 87 (9.01). HRMS calculated for $C_{12}H_{14}F_2N_2OS$: 272.0795; found: 272.0791.

3.3.4. 2-(4-Fluorophenylimino)-4,4-dimethyl-thiazolidine (*3d*)

2-(4-Fluorophenylimino)-4,4-dimethyl-thiazolidine (**3d**) yield 61%, mp 209–210 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 1.39 (s, 6H, CH_3) 3.18 (s, 2H, H-5), 7.00 (t, 2H, $J_{2'3'} = J_{5'6'} = 8.3$ Hz, $J_{4'3'} = J_{4'5'} = 8.8$ Hz, H-3′ and H-5′), 7.36 (br s, 1.2H, H-2′ and H-6′). IR(KBr) (cm^{-1}): 3100 (NH), 2950, 2825 (C–H), 1630 (C=N), 1590, 1500 (Ph), 1320, 1210 (C–S), 1190, 1170, 850, 760, 650. MS (EI, 70 eV) *m/z* (%): 225 (23.84) [*M* + 1], 224 (45.53) [*M*], 209 (100.00) [*M*–CH_3], 137 (11.80), 136 (27.87), 88 (12.72). HRMS calculated for $C_{11}H_{13}FN_2S$: 224.0783; found: 224.0788.

*3.3.5. 2-(4-Fluorophenylimino)-4-ethyl-4-hydroxymethyl-thiazolidine (**3e**)*

2-(4-Fluorophenylimino)-4-ethyl-4-hydroxymethyl-thiazolidine (**3e**) yield 42%, mp 154–155 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 0.99 (t, 3H, $J = 7.5$ Hz, CH_3), 1.69 (m, 2H, CH_2), 3.06 (d, 1H, $J = 10.9$ Hz, $H_{a(b)}$-5), 3.36 (d, 1H, $J = 10.9$ Hz, $H_{b(a)}$-5), 3.52 (d, 1H, $J = 10.8$ Hz, $H_{a(b)}$–CH_2OH), 3.59 (d, 1H, $J = 10.8$ Hz, $H_{b(a)}$–CH_2OH), 7.00 (t, 2H, $J_{2'3'} = J_{6'5'} = 8.9$ Hz, $J_{4'5'} = J_{4'3'} = 8.8$ Hz, H-3′ and H-5′), 7.49 (br s, 1.7H, H-2′ and H-6′). IR (KBr) (cm^{-1}): 3300 (OH), 3100 (NH), 2875, 1640 (C=N), 1500 (Ph), 1200, 1050, 850. MS (EI, 70 eV) *m/z* (%): 254 (5.61) [*M*], 223 (100.00) [*M*–CH_2OH], 195 (4.31) [*M*–HCHO–C_2H_5], 102 (23.28). HRMS calculated for $C_{12}H_{15}FN_2OS$: 254.0889; found: 254.0880.

*3.3.6. 2-(4-Fluorophenylimino)-tetrahydro-thiazolidine (**3f**)*

2-(4-Fluorophenylimino)-tetrahydro-thiazolidine (**3f**) yield 84%, mp 153–154 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 3.32 (t, 2H, $J = 7.2$ Hz, H-5), 3.92 (s, 2H, H-4), 7.01 (m, 2H, H-3′ and H-5′), 7.40 (br s, 2H, H-2′ and H-6′). IR (KBr) (cm^{-1}): 3125 (NH), 2800, 1630 (C=N), 1600, 1500 (Ph), 1300, 1200, 1180, 780, 620. MS (EI, 70 eV) *m/z* (%): 196 (93.04) [*M*], 168 (11.72) [*M*–CH_2=CH_2], 149 (12.52) [*M*–SCH_3], 136 (100.00) [*M*–C_2H_4S], 122 (32.36) [*M*–C_2H_4NS], 109 (22.65) [*M*–C_3H_5NS], 95 (17.34). HRMS calculated for $C_9H_9FN_2S$: 196.0470; found: 196.0479.

*3.3.7. 2-(2,3,4-Trifluorophenylimino)-tetrahydro-thiazolidine (**3g**)*

2-(2,3,4-Trifluorophenylimino)-tetrahydro-thiazolidine (**3g**) yield 80%, mp 151–152 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 3.39 (t, 2H, $J = 7.0$ Hz, H-5), 3.74 (t, 2H, $J = 7.0$ Hz, H-4), 6.90 (br s, 1H, H-6′), 7.06 (q, 1H, $J_{4'5'} = 10.4$ Hz, $J_{6'5'} = 10.4$ Hz, $J_{3'5'} = 9.2$ Hz, H-5′). IR (KBr) (cm^{-1}): 3150 (NH), 2850, 1650 (C=N), 1630, 1600, 1500, 1450 (Ph), 1320, 1230, 1040, 980. MS (EI, 70 eV) *m/z* (%): 232 (100.00) [*M*], 213 (77.11) [*M*–F], 185 (13.55) [*M*–SCH_3], 172 (88.86) [*M*–SC_2H_4], 158 (25.37) [*M*–C_2H_4NS], 145 (12.94), 61 (9.61). HRMS calculated for $C_9H_7F_3N_2S$: 232.0282; found: 232.0296.

*3.3.8. 2-(2,3,4-Trifluorophenylimino)-4-ethyl-4-hydroxymethyl-thiazolidine (**3h**)*

2-(2,3,4-Trifluorophenylimino)-4-ethyl-4-hydroxymethyl-thiazolidine (**3h**) yield 52%, mp 165–166 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 1.00 (t, 3H, $J = 7.5$ Hz, CH_3), 1.78 (q, 2H, $J = 7.5$ Hz, CH_2), 3.31 (d, 1H, $J = 11.1$ Hz, $H_{a(b)}$-5), 3.53 (d, 1H, $J = 11.1$ Hz, $H_{b(a)}$-5), 3.56 (d, 1H, $J = 11.1$ Hz, $CH_{2a(2b)}OH$), 3.71 (d, 1H, $J = 11.1$ Hz, $CH_{2b(2a)}OH$), 6.87 (br s, 0.6H, H-6′), 7.05 (q, 1H, $J_{2'5'} = 9.1$ Hz, $J_{4'5'} = 10.1$ Hz, $J_{3'5'} = 8.4$ Hz, H-5′). IR (KBr) (cm^{-1}): 3300 (OH), 3100, 2875, 1630 (C=N), 1500 (Ph), 1250 (C–S), 1220, 1050, 980, 820. MS (EI, 70 eV) *m/z* (%): 290 (7.33) [*M*], 259 (100.00) [*M*–CH_2OH], 231 (36.64) [*M*–C_3H_7O], 172 (6.08), 102 (24.29), 87 (9.46). HRMS calculated for $C_{12}H_{13}F_3N_2OS$: 290.0701; found: 290.0702.

*3.3.9. 2-(2,3,4-Trifluorophenylimino)-4,4-dimethyl-thiazolidine (**3i**)*

2-(2,3,4-Trifluorophenylimino)-4,4-dimethyl-thiazolidine (**3i**) yield 73%, mp 195–196 °C. ^{1}H NMR (CD_3COCD_3, 500 MHz) δ: 1.43 (s, 6H, CH_3), 3.22 (s, 2H, H-5), 6.81 (br s, 0.36H, H-2′ and H-6′), 7.10 (q, 1H, $J_{4'5'} = 8.9$ Hz, $J_{6'5'} = 8.9$ Hz, $J_{3'5'} = 8.3$ Hz, H-5′). IR(KBr) (cm^{-1}): 3150 (NH), 2950, 2875, 1620 (C=N), 1600, 1500, 1300, 1260, 1230 (C–S), 1000, 820. MS (EI, 70 eV) *m/z* (%): 260 (79.16) [*M*], 245 (100.00) [*M*–CH_3], 213 (6.70) [*M*–SCH_3], 172 (28.62), 147 (12.96), 88 (29.87), 55 (29.98). HRMS calculated for $C_{11}H_{11}F_3N_2S$: 260.0595; found: 260.0612.

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