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Syntheses, structures and bioactivities of fluorine-containing phenylimino-thia(oxa)zolidine derivatives as agricultural bioregulators

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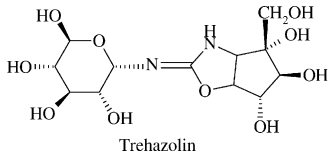
Abstract

From insight into the structure of trehazolin as trehalase inhibitor, six series of fluorine-containing phenylimino-thiazolidines (oxazolidines) derivatives were designed and prepared through a convenient synthesis of fluoroaryl isothiocyanate and a one-pot facile synthesis in high yield of fluorophenyl aminobenzoxazoles by cyclodesulfurization. The structures of the target compounds were confirmed with using IR, NMR, MS and elemental analysis. Their X-ray crystal analysis suggested that there were novel intermolecular ($sp^2CF\cdots H_3C$–) and intramolecular ($sp^2CF\cdots HN$) hydrogen bonds between the fluorine atom on benzene ring and hydrogen atom of methyl group or amino group on five-membered heterocycle. Their fungicidal activities against *Rhizoctonia solani* and *Pyricuraria oryzae* at 100 ppm were determined.

Keywords: Fluoro group; Phenylimino-thiazolidine (oxazolidine); Agricultural bioregulators; Hydrogen bonding

1. Introduction

Natural trehazolin, just like Validamycin A [1] that has been commercialized and is used to control blight sheath of rice caused by the plant pathogenic fungus *Rhizoctonia solani*, is a slow- and tight-binding inhibitor of trehalase [2]. Trehazolin also shows potential fungicidal activity to control *R. solani* at 100 ppm [3].



Trehazolin

Recently, a variety of the reports regarding synthesis or modification of the trehazolin derivatives have been presented due to the chemical and biological interests [2,4–7]. But, the structure of trehazolin and its analogues are complicated and their syntheses were very difficult. Shiozaki reported that trehazolin was obtained from a 15-step synthesis starting from D-glucose, which was a convergent strategy [8–12]. In addition, trehazolin and its analogues had high inhibition activities in vitro, and only showed low activities in vivo because of too many hydrophilic hydroxyl groups in their structures. So far there have been few reports about an unnatural product, e.g. fluorinated compound, which mimic trehazolin as trehalase inhibitor to show fungicidal activities, which have relatively simple structures and can be prepared easily.

Trehalase is a very specific enzyme that hydrolyzes trehalose, which is a main source of glucose in insects and fungi, to two glucose units and is widely distributed in microorganisms, insects, plants and animals [13,2]. Besides trehazolin [14] some other trehalase inhibitors have been isolated from natural sources, such as deoxynojirimycin [15], salbostain [16], validamycins [17], and validoxylamines [18]. Of course, trehazolin is the most potent one among natural products. A notable feature of this inhibition

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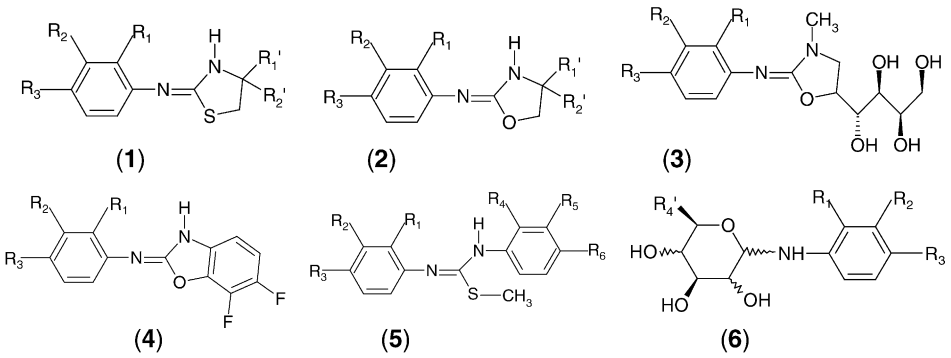
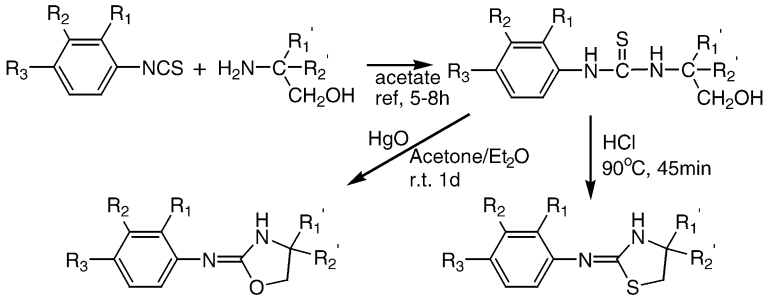


Fig. 1. The structures of designed compounds **1–6**.



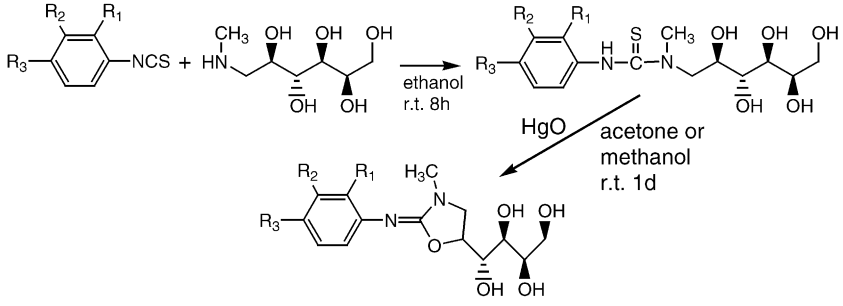
Scheme 1.

is the formation of trehazolin–trehalase complex through the bridgehead nitrogen in trehazolin and the carbonyl group in trehalase [19], and the hydroxyl groups in trehazolin were topologically essential for its tight binding to the active sites of trehalase through hydrogen bonds [20]. It is well known that fluorine-containing compounds usually exhibit significant agricultural bioactivity owing to their unique property, such as high thermal stability, lipophilicity and ability to form hydrogen bonds with the active site of some enzyme [21]. The incorporation of polyfluorophenyl groups would increase the precursor's hydrophobicity and penetrating ability. Thus, on the basis of trehazolin structural model (a N=C–N unit, heterocyclic moiety and polyhydroxyl groups) [20,21] six series of fluorine-containing compounds including phenylimino-thiazo(oxazo)lidines (**1**–**3**) [22,23], phenylimino-benzoxazolidines (**4**) [24], *N*,*N*′-diphenyl carbamidothioates (**5**), and pyranoaniline derivatives (**6**) [25] were designed and synthesized, their structures and fungicidal activities were also investigated. The structures of **1–6** are shown in Fig. 1.

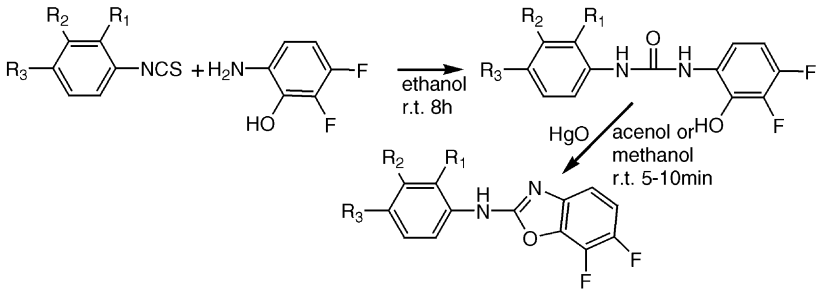
2. Results and discussion

2.1. Synthesis of fluorophenyl imino-thiazo(oxazo)lidines and analogues

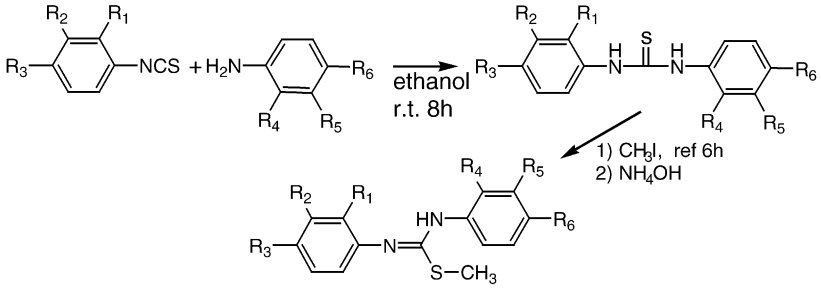
By a facile and convenient method, novel fluorine-containing phenylimino-thiazo(oxazo)lidines (**1–3**) were synthesized as shown in Schemes 1 and 2. Phenylimino-



Scheme 2.



Scheme 3.



Scheme 4.

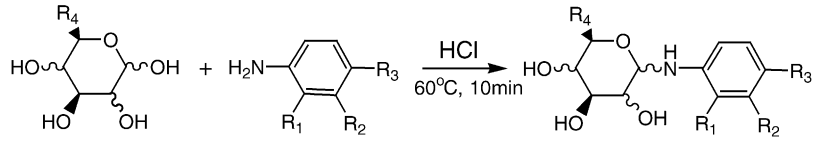
benzoxazolidines (**4**), *N*,*N*′-diphenyl carbamidothioates (**5**), pyranoaniline derivatives (**6**) were prepared as shown in Schemes 3–5, respectively. The substituents of compounds **1**–**6** are listed in Table 1. The structures of compounds **1**–**6** were confirmed by using NMR, IR, MS and elemental analysis [22–25,31,36], which are listed in Table 2.

The syntheses of the target compounds **1**–**5** need the key intermediates of fluorophenyl isothiocyanates. Aryl isothiocyanates, which were frequently used for the preparation of medicine or pesticides, are usually synthesized from arylamines through treatment with carbon disulfide, aqueous ammonia and lead nitrate [26] or by treatment with thiophosgene [27], the other synthetic methods were from monoarylthioureas [27], phosphoramidates [28], arylimino-dithiazoles [29] or amine (modified Kaluza method) [30]. However, the most of these methods are laborious and suffer from low yields, and its very difficult for us to follow the known synthetic methods for synthesis of fluoroaryl isothiocyanates, as the presence of too strong electron-withdrawing fluorine. Therefore, from the insight to synthesis of alkylisothiocyanates, a more straightforward and convenient synthetic route in one-step and high yield was provided here for fluoroaryl isothiocyanates from fluoroarylamines in the presence of CS_2, NaOH and ClCOOEt (Scheme 6) [31].

2-Aryl aminobenzoxazoles were generally synthesized by cyclodesulfurization of *N*-(2-hydroxyphenyl)-*N*′-phenylthioureas with nickel peroxide [32], potassium superoxide [33] and dicyclohexylcarbodiimide [34], or by treatment of 2-chlorobenzoxazole with aniline in THF [35]. It was also very difficult for us to synthesize fluorophenyl aminobenzoxazoles with using the known synthetic method for non-fluoro-counterpart, as the presence of too strong electron-withdrawing fluoro-group. From the insight to cyclization of 2-alkyl aminooxazole, we established here a one-pot facile synthesis (2–10 min) in high yield (82–95%) of fluorophenyl aminobenzoxazoles by the cyclodesulfurization with HgO (Scheme 7) [36].

2.2. Intermolecular hydrogen bond with F as acceptors

The X-ray structures of some compounds **1**–**6** were obtained. An intermolecular hydrogen bonding (aromatic –$CH_3 \cdots FCsp^2$) between the fluorine atom on benzene ring



Scheme 5.

Table 1
The substituents of compounds **1–6**

Number	R_1	R_2	R_3	R'_1 (R_4)	R'_2 (R_5)	R_6
1a	H	Cl	F	CH_2OH	CH_2OH	–
1b	F	F	F	CH_2OH	CH_2OH	–
1c	H	Cl	H	CH_2OH	CH_2OH	–
1d	F	H	H	H	H	–
1e	F	H	H	CH_3	CH_3	–
1f	F	H	F	CH_3	CH_3	–
1g	F	H	H	CH_2OH	C_2H_5	–
1h	F	H	F	CH_2OH	C_2H_5	–
1i	H	H	F	H	H	–
1j	F	F	F	H	H	–
1k	F	F	F	CH_3	CH_3	–
3a	F	H	H	–	–	–
3b	H	H	F	–	–	–
3c	H	Cl	F	–	–	–
3d	F	H	F	–	–	–
3e	F	F	F	–	–	–
3f	H	Cl	H	–	–	–
3g	H	H	H	–	–	–
3h	H	H	OH	–	–	–
5a	F	F	F	F	H	F
5b	F	F	F	F	F	F
5c	F	F	F	H	F	F
5d	F	H	F	F	H	F
5e	F	H	F	H	F	F
5f	F	H	H	F	H	H
5g	H	H	F	H	H	F
5h	F	H	Cl	F	H	Cl
5i	H	Cl	F	H	Cl	F
2a	H	Cl	F	CH_2OH	CH_2OH	–
2b	F	H	H	CH_2OH	CH_2OH	–
2c	F	F	F	CH_2OH	CH_2OH	–
2d	F	H	H	H	H	–
2e	H	H	F	CH_2OH	CH_2OH	–
4a	F	H	H	–	–	–
4b	H	H	F	–	–	–
4c	H	Cl	F	–	–	–
4d	F	H	F	–	–	–
4e	F	F	F	–	–	–
4f	Cl	H	H	–	–	–
4g	H	Cl	H	–	–	–
4h	F	H	Cl	–	–	–
4i	H	H	OH	–	–	–
6a	F	H	F	β-D-Glucopyranosyl	–	–
6b	H	F	F	β-D-Glucopyranosyl	–	–
6c	H	H	F	β-D-Glucopyranosyl	–	–
6d	F	F	F	β-D-Glucopyranosyl	–	–
6e	H	Cl	F	β-D-Glucopyranosyl	–	–
6f	H	F	F	β-D-Galactopyranosyl	–	–
6g	H	F	F	β-D-Mannopyranosyl	–	–
6h	H	F	F	β-D-Xylopyranosyl	–	–
6i	H	Cl	F	β-D-Galactopyranosyl	–	–
6j	H	Cl	F	β-D-Mannopyranosyl	–	–
6k	H	Cl	F	β-D-Xylopyranosyl	–	–

and hydrogen atom of a methyl group on five-membered heterocycle was observed on X-ray crystal stacking spectrum of **1k**. The distance of hydrogen bond $-CH_3\cdots F$ is 2.555 Å, and the angle of $C–H\cdots F$ is 164.5° (Fig. 2). The distance and angle all reach to the condition for the formation of hydrogen bonds. When we synthesized *o*-fluorophenyl thiazolidine for investigation of hydrogen bonding with fluorine as an acceptor, an intramolecular hydrogen bonding ($NH\cdots FCsp^2$) between the fluorine atom on benzene ring and hydrogen atom of an amino group on five-membered heterocycle was also observed from its X-ray crystal stacking spectrum, in which there are two different conformations in one crystal unit and also fluorine group is unlocated on 2- or 6-position (labeled as F1 and F1′or F2 and F2′) in each conformation. The distance of hydrogen bond $NH\cdots F$ is 2.470 Å, and the angle of $N–H\cdots F$ is 115° (Fig. 3). Many bioorganic chemists and biochemists believed that the formation of intermolecular $F\cdots H$ hydrogen bonding, e.g. $O–H\cdots FC$ and $N–H\cdots FC$ hydrogen bonds might be important in the binding of fluorinated substrates to enzyme active sites [37]. Nevertheless, the role of organic fluorine atoms as hydrogen bond acceptors in at least some systems remains controversial [37], in part because there are few detailed studies of ''unconstrained'' intermolecular $O–H\cdots FC$ and $N–H\cdots FC$ hydrogen bonds. So far, the reports about hydrogen bonds between fluorine and hydrogen atom were only limited to few molecules, such as $CH_4\cdots F–CH_3$ [38], $O–H\cdots F_3C–$ [37], $sp^3CH\cdots FCsp^3$ hydrogen bonding in oxirane-trifluoromethane dimer [39]. Few reports were published on CH_3 or $NH\cdots FCsp^2$ hydrogen bonding, except for a relative investigation on arene-polyfluoroarene π–π interaction for $FCsp^2$ [40].

2.3. Fungicidal activity

The fungicidal activities of the above compounds against *R. solani* and *Pyricuraria oryzae* were determined at the concentration of 100 ppm according to the same method as the literature [41], and the fungicidal data are listed in Table 2. Their bioactivities depend upon the number and position of fluorine groups on the aryl rings. The fungicidal activities of compounds in series **1**, **2** and **4** are lower than those in series **3**, **5** and **6**. Those in series **3** and **5** are worth studying further. When numbers of fluorine are introduced into aryl ring, e.g. **5a–i**, the fungicidal activities increased significantly. The fungicidal activities of several compounds in series **5** against *R. solani* and *P. oryzae* can reach 100%. In addition, some of series **6** exhibited definite fungicidal activity at 1000 ppm against *R. solani* in vivo.

3. Experimental details

Melting points were obtained with an electrothermal digital apparatus 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 (^1H 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

Table 2
Structural characterization and fungicidal activity of compound

Number	Spectrum data	Fungicidal activity at 100 ppm (%)	
		R. solani	*P. oryzae*
1a	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: H-2′ (no signal), H-6′ (no signal), 7.17 (t, $J_{4',5'} = 9.0$ Hz, $J_{5',6'} = 9.0$ Hz, 1H, H-5′), 3.71 and 3.67 (ABq, $J_{gem} = 11.0$ Hz, 4H, CH_2OH), 3.32 (s, 2H, SCH_2). IR (KBr), ν: 3280 (OH), 3100 (NH), 1640 (C=N), 1600, 1495 (Ph), 1190 cm^{-1} (C–S). Anal. Calcd. for $C_{11}H_{12}ClFN_2O_2S$ (%): C, 45.44; H, 4.13; N, 9.64. Found: C, 45.21; H, 4.28; N, 10.49	0	0
1b	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: H-6′ (no signal), 7.05 (q, $J_{3',5'} = 9.2$ Hz, $J_{4',5'} = 9.2$ Hz, $J_{5',6'} = 9.2$ Hz, 1H, H-5′), 3.75 and 3.67 (ABq, $J_{gem} = 11.0$ Hz, 4H, CH_2OH), 3.30 (s, 2H, SCH_2). IR (KBr), ν: 3280 (OH), 3100 (NH), 1630 (C=N), 1505 (Ph), 1220 cm^{-1} (C–S). Anal. Calcd. for $C_{11}H_{11}F_3N_2O_2S$ (%): C, 45.21; H, 3.77; N, 9.59. Found: C, 45.19; H, 3.66; N, 9.67	0	0
1c	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: H-2′ (no signal), H-6′ (no signal), 7.24 (t, $J_{4',5'} = J_{5',6'} = 8.0$ Hz, 1H, H-5′), 7.00 (d, $J_{4',5'} = 8.0$ Hz, 1H, H-4′), 3.71 and 3.67 (ABq, $J_{gem} = 11.0$ Hz, 4H, CH_2OH), 3.30 (s, 2H, SCH_2). IR (KBr), ν: 3280 (OH), 3100 (NH), 1640 (C=N), 1580, 1460 cm^{-1} (Ph). MS (EI, 70 eV), m/z (%): 274 ($M^+ + 2$) (38), 272 (M^+) (100), 243 (29), 241 (77), 213 (7), 211 (19), 129 (14), 127 (43), 31 (26). Anal. Calcd. for $C_{11}H_{13}ClN_2O_2S$ (%): C, 48.44; H, 4.80; N, 10.27. Found: C, 48.68; H, 4.76; N, 10.24	7.1	15.4
1d	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.34 (br s, 0.59H, H-6′), 7.05 (m, 2H, H-3′ and H-5′), 6.98 (m, 1H, H-4′), 3.73 (s, 2H, NCH_2), 3.31 (s, 2H, SCH_2). IR (KBr), ν: 3100 (NH), 1630 (C=N), 1600, 1495 (Ph), 1230 cm^{-1} (C–S). MS (EI, 70 eV), m/z (%): 198 (40) ($M^+ + 2$), 197 (94) ($M^+ + 1$), 196 (100) (M^+), 195 (69), 176 (38). Anal. Calcd. for $C_9H_9FN_2S$ (%): C, 55.08; H, 4.62; N, 14.28. Found: C, 55.32; H, 4.53; N, 14.38	21.4	7.7
1e	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: H-6′ (no signal), 7.05 (m, 2H, H-3′ and H-5′), 6.99 (m, 1H, H-4′), 3.16 (s, 2H, SCH_2), 1.42 (s, 6H, CH_3). IR (KBr), ν: 3100 (NH), 1630 (C=N), 1600, 1500 (Ph), 1250 cm^{-1} (C–S). Anal. Calcd. for $C_{11}H_{13}FN_2S$ (%): C, 58.90; H, 5.84; N, 12.49. Found: C, 58.96; H, 5.83; N, 12.57	7.1	7.7
1f	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: H-6′ (no signal), 7.05 (m, 2H, H-3′ and H-5′), 6.99 (m, 1H, H-4′), 3.16 (s, 2H, SCH_2), 1.42 (s, 6H, CH_3). IR (KBr), ν: 3100 (NH), 1630 (C=N), 1600, 1500 (Ph), 1250 cm^{-1} (C–S). Anal. Calcd. for $C_{11}H_{13}FN_2S$ (%): C, 58.90; H, 5.84; N, 12.49. Found: C, 58.96; H, 5.83; N, 12.57	0	7.7
1g	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.32 (br s, 1H, H-6′), 7.06 (m, 2H, H-3′ and H-5′), 6.99 (m, 1H, H-4′), 3.65 and 3.55 (ABq, $J_{gem} = 10.8$ Hz, 2H, CH_2OH), 3.55 and 3.14 (ABq, $J_{gem} = 11.0$ Hz, 2H, SCH_2), 1.76 (m, 2H, CH_2), 0.99 (t, $J = 7.4$ Hz, 3H, CH_3). IR (KBr), ν: 3330 (OH), 3170 (NH), 1630 (C=N), 1600, 1495 (Ph), 1230 cm^{-1} (C–S). MS (EI, 70 eV), m/z (%): 255 ($M^+ + 1$) (32), 254 (10), 225 (12), 224 (22), 223 (100), 31 (19). Anal. Calcd. for $C_{12}H_{15}FN_2OS$ (%): C, 56.67; H, 5.94; N, 11.02. Found: C, 56.84; H, 5.90; N, 10.99	57.1	100
1h	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.40 (br s, 1H, H-6′), 6.98 (t, $J_{2',3'} = J_{3',4'} = 9.8$ Hz, 1H, H-3′), 6.87 (t, $J_{4',5'} = J_{5',6'} = 8.6$ Hz, 1H, H-5′), 3.66 and 3.56 (ABq, $J_{gem} =$ 10.8 Hz, 2H, CH_2OH), 3.34 and 3.12 (ABq, $J_{gem} = 11.0$ Hz, 2H, SCH_2), 1.75 (m, 2H, CH_2), 0.99 (t, $J = 7.5$ Hz, 3H, CH_3). IR (KBr), ν: 3300 (OH), 3100 (NH), 1640 (C=N), 1505 (Ph), 1240 cm^{-1} (C–S). MS (EI, 70 eV), m/z (%): 273 ($M^+ + 1$) (13), 272 (17), 243 (22), 242 (39), 241 (100), 225 (17), 102 (51), 101 (17), 31 (17). Anal. Calcd. for $C_{11}H_{14}F_2N_2OS$ (%): C, 52.93; H, 5.18; N, 10.29. Found: C, 52.72; H, 5.16; N, 10.36	31.4	23.1
1i	^{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), ν: 3125 (NH), 2800, 1630 (C=N), 1600, 1500 (Ph), 1300, 1200, 1180, 780, 620 cm^{-1}. MS (EI, 70 eV), m/z (%): 196 (M^+) (93.04) 168 ($M^+ - CH_2{=}CH_2$) (11.72), 149 ($M^+ - SCH_3$) (12.52), 136 ($M^+ - SC_2H_4$) (100), 122 ($M^+ - C_2H_4NS$) (32.36), 109 ($M^+ - C_3H_5NS$) (22.65), 95 (C_6H_5F) (17.34). Anal. Calcd. for $C_9H_9FN_2S$ (%): C, 55.14; H, 4.63; N, 14.29. Found: C, 55.20; H, 4.73; N, 14.39	60	87.5
1j	^{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), ν: 3150 (NH), 2850, 1650 (C=N), 1630, 1600, 1500, 1450 (Ph), 1320, 1230, 1040, 980 cm^{-1}. MS (EI, 70 eV), m/z (%): 232 (M^+) (100), 213 ($M^+ - F$) (77.11), 185 ($M^+ - SCH_3$) (13.55), 172 ($M^+ - SC_2H_4$) (88.86), 158 ($M^+ - C_2H_4NS$) (25.37), 145 ($C_6H_5F_3N$) (12.94), 61 (C_2H_5FS) (9.61). Anal. Calcd. for $C_9H_7F_3N_2S$ (%): C, 46.58; H, 3.04; N, 12.07. Found: C, 46.42; H, 3.13; N, 11.00	80	85.7

Table 2 (*Continued*)

Number	Spectrum data	Fungicidal activity at 100 ppm (%)	
		R. solani	*P. oryzae*
1k	^{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), ν: 3150 (NH), 2950, 2875, 1620 (C=N), 1600, 1500 (Ph), 1300, 1260, 1230 (C–S), 1000, 820 cm^{-1}. MS (EI, 70 eV), *m/z* (%): 260 (M^+) (79.16), 245 ($M^+ - CH_3$) (100), 213 ($M^+ - SCH_3$) (6.7), 172 ($F_3C_6H_5N$=C–NH) (28.62), 147 ($F_3C_6H_5NH_2$) (12.96), 88 (($CH_3)_2CCH_2S$) (29.87), 55 (C_4H_7) (29.98). Anal. Calcd. for $C_{11}H_{11}F_3N_2S$ (%): C, 50.80; H, 4.26; N, 10.77. Found: C, 50.61; H, 4.30; N, 10.63	0	0
2a	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.80 (br s, 1H, H-6′), 7.37 (br s, 1H, H-2′), 7.17 (t, $J_{4',5'} = 9.0$ Hz, $J_{5',6'} = 9.0$ Hz, 1H, H-5′), 4.27 (s, 2H, OCH_2), 3.61 (s, 4H, CH_2OH). IR (KBr), ν: 3250 (OH), 3108 (NH), 1660 (C=N), 1610, 1505 (Ph), 1260 cm^{-1} (C–S). MS (EI, 70 eV), *m/z* (%): 276 (M^+ + 2) (4), 274 (M^+), 245 (34), 243 (100), 147 (4), 145 (12), 31 (21). Anal. Calcd. for $C_{11}H_{12}ClFN_2O_3$ (%): C, 48.09; H, 4.37; N, 10.20. Found: C, 47.93; H, 4.52; N, 10.33	43.3	15.4
2b	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.60 (br s, 1H, H-6′), 7.07 (m, 2H, H-3′ and H-5′), 6.95 (m, 1H, H-4′), 4.29 (s, 2H, OCH_2), 3.64 (s, 4H, CH_2OH). IR (KBr), ν: 3230 (OH), 3100 (NH), 1670 (C=N), 1605, 1495 (Ph), 1250 cm^{-1} (C–S). MS (EI, 70 eV), *m/z* (%): 242 (M^* + 2) (73), 241 (M^* + 1) (100), 240 (M^*) 14), 210 (10), 209 (100), 179 (9), 110 (8), 31 (24). Anal. Calcd. for $C_{11}H_{13}FN_2O_3$ (%): C, 55.00; H, 5.42; N, 11.67. Found: C, 55.06; H, 5.33; N, 11.63	38.6	30.8
2c	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: H-6′ (no signal), 6.98 (m, 1H, H-5′), 4.52 (s, 2H, OCH_2), 3.69 and 3.65 (ABq, J_{gem} = 11.4 Hz, 4H, CH_2OH). IR (KBr), ν: 3300 (OH), 1700 (C=N), 1510 (Ph), 1270 cm^{-1} (C–S). MS (EI, 70 eV), *m/z* (%): 277 (M^+ + 1) (14), 276 (M^+) (100), 245 (13), 195 (7), 194 (83), 176 (31), 162 (7), 148 (9), 31 (17). Anal. Calcd. for $C_{11}H_{11}F_3N_2O_3$ (%): C, 47.83; H, 3.99; N, 10.14. Found: C, 47.66; H, 3.71; N, 10.38	0	0
2d	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.36 (br s, 1H, H-6′), 7.03 (m, 2H, H-3′ and H-5′), 6.93 (m, 1H, H-4′), 4.41 (t, J_{45} = 7.8 Hz, 2H, OCH_2), 3.70 (t, J_{45} = 7.8 Hz, 2H, NCH_2). IR (KBr), ν: 3070 (NH), 1690 (C=N), 1600, 1500 (Ph), 1230 cm^{-1} (C–S). MS (EI, 70 eV), *m/z* (%): 182 (9) (M^+ + 2), 181 (88) (M^+ + 1), 180 (100) (M^+), 161 (25), 137 (30), 122 (64), 109 (22), 95 (12), 83 (22). Anal. Calcd. for $C_9H_9FN_2O$ (%): C, 60.00; H, 5.03; N, 15.55. Found: C, 59.77; H, 5.02; N, 15.52	7.1	0
2e	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.57 (br s, 1.46H, H-2′ and H-6′), 7.00 (t, $J_{2',3'} = J_{5',6'} = 8.9$ Hz, $J_{3',4'} = J_{4',5'} = 8.9$ Hz, 2H, H-3′ and H-5′), 4.23 (s, 2H, OCH_2), 3.62 and 3.64 (ABq, J_{gem} = 11.0 Hz, 4H, CH_2OH). MS (EI, 70 eV), *m/z* (%): 242 (M^* + 2) (86), 241 (M^* + 1) (100), 240 (M^*) (26), 210 (22), 209 (63), 179 (22), 110 (19), 31 (29). IR (KBr), ν: 3205 (OH), 3100 (NH), 1655 (C=N), 1600, 1510 (Ph), 1220 cm^{-1} (C–S). Anal. Calcd. for $C_{11}H_{13}FN_2O_3$ (%): C, 55.00; H, 5.42; N, 11.67. Found: C, 55.16; H, 5.37; N, 11.58	7.9	0
2f	^{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), ν: 3100 (NH), 2950, 2825 (C–H), 1630 (C=N), 1590, 1500 (Ph), 1320, 1210 (C–S), 1190, 1170, 850, 760, 650 cm^{-1}. MS (EI, 70 eV), *m/z* (%): 225 (M^+ + 1) (23.84), 224 (M^+) (45.53), 209 ($M^+ - CH_3$) (100), 137 (FC_6H_5N =C–NH_2) (11.80), 136 (FC_6H_5N=CNH) (27.87), 88 (($CH_3)_2CCH_2S$) (12.72). Anal. Calcd. for $C_{11}H_{13}FN_2S$ (%): C, 53.60; H, 5.85; N, 12.50. Found: C, 53.68; H, 5.90; N, 12.61	0	7.7
3a	^{1}H NMR (D_2O, 500 MHz), δ: 7.05–7.11 (m, 4H, ArH), 4.72 (m, 1H, H-5), 3.48–3.91 [m, 7H, CH(OH)CH(OH)CH(OH)CH_2OH and NCH_2], 2.91 (s, 3H, CH_3N). IR (KBr), ν: 3370 (OH), 1670 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 314 (M^+) (1), 137 (5), 111 (6), 44 (100), 31 (28), 15 (10). Anal. Calcd. for $C_{14}H_{19}FN_2O_5$ (%): C, 53.50; H, 6.09; N, 8.91. Found: C, 53.72; H, 6.14; N, 8.87	38.6	30.8
3b	^{1}H NMR (D_2O, 500 MHz), δ: 7.01 (m, 4H, ArH), 4.70 (m, 1H, H-5), 3.40–3.90 [m, 7H, CH(OH)CH(OH)CH(OH)CH_2OH and NCH_2], 2.87 (s, 3H, CH_3N). IR (KBr), ν: 3300 (OH), 1665 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 314 (M^+) (1), 202 (6), 137 (10), 111 (6), 44 (100), 31 (22), 15 (23). Anal. Calcd. for $C_{14}H_{19}FN_2O_5$ (%): C, 53.50; H, 6.09; N, 8.91. Found: C, 53.84; H, 6.07; N, 8.85	64.3	69.2
3c	^{1}H NMR (D_2O, 500 MHz), δ: 7.16 (dd, $J_{2',4'} = 6.7$ Hz, $J_{2',6'} = 2.6$ Hz, 1H, H-2′), 7.10 (t, $J_{4',6'} = 9.0$ Hz, $J_{5',6'} = 9.0$ Hz, 1H, H-6′), 6.93 (m, 1H, H-5′), 4.74 (m, 1H, H-5), 3.51–3.93 [m, 7H, CH(OH)CH(OH)CH(OH)CH_2OH and NCH_2], 2.91 (s, 3H, CH_3N). IR (KBr), ν: 3400 (OH), 1680 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 350 (M^+ + 2) (2), 348 (M^+) (6), 179 (9), 145 (12), 117 (11), 44 (100), 31 (13), 15 (23). Anal. Calcd. for $C_{14}H_{18}ClFN_2O_5$ (%): C, 48.22; H, 5.20; N, 8.03. Found: C, 48.51; H, 5.30; N, 8.16	64.3	38.5
3d	^{1}H NMR (D_2O, 500 MHz), δ: 6.96 (td, $J_{2',6'} = 6.3$ Hz, $J_{4',6'} = 9.1$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-6′), 6.84 (t, $J_{2',3'} = 10.7$ Hz, $J_{3',4'} = 10.7$ Hz, 1H, H-3′), 6.76 (t, $J_{4',5'} = 9.1$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-5′), 4.62 (m, 1H, H-5), 3.37–3.81 [m, 7H, CH(OH)CH(OH)CH(OH)CH_2OH and NCH_2], 2.91 (s, 3H, CH_3N). IR (KBr), ν: 3400 (OH), 1680 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 332 (M^+) (2), 202 (48), 201 (23), 200 (38), 199 (28), 198 (18), 144 (100), 31 (27), 15 (12). Anal. Calcd. for $C_{14}H_{18}F_2N_2O_5$ (%): C, 50.60; H, 5.46; N, 8.43. Found: C, 50.54; H, 5.42; N, 8.37	0	0

Table 2 (*Continued*)

Number	Spectrum data	Fungicidal activity at 100 ppm (%)	
		R. solani	*P. oryzae*
3e	^{1}H NMR (D_2O, 500 MHz), δ: 6.90 (m, 1H, H-6′), 6.79 (m, 1H, H-5′), 4.70 (m, 1H, H-5), 3.44–3.86 [m, 7H, CH(OH)CH(OH)CH(OH)CH_2OH and NCH_2], 2.87 (s, 3H, CH_3N). IR (KBr), ν: 3400 (OH), 1670 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 350 (M^+) (100), 117 (14), 44 (25), 31 (5), 15 (2). Anal. Calcd. for $C_{14}H_{17}F_3N_2O_5$ (%): C, 48.00; H, 4.89; N, 8.00. Found: C, 47.62; H, 4.83; N, 8.04	73.7	38.5
3f	^{1}H NMR (D_2O, 500 MHz), δ: 7.19 (t, $J_{4',5'} = 8.0$ Hz, $J_{5',6'} = 8.0$ Hz, 1H, H-5′), 7.05 (s, 1H, H-2′), 7.01 (d, $J_{5',6'} = 8.0$ Hz, 1H, H-6′), 6.91 (d, $J_{4',5'} = 8.0$ Hz, 1H, H-4′), 4.70 (m, 1H, H-5), 3.41–3.88 [m, 7H, CH(OH)CH(OH)CH(OH)CH_2OH and NCH_2], 2.84 (s, 3H, CH_3N). IR (KBr), ν: 3390 (OH), 1660 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 332 (M^+ + 2) (38), 330 (M^+) (100), 177 (29), 116 (22), 44 (64). Anal. Calcd. for $C_{14}H_{19}ClN_2O_5$ (%): C, 50.84; H, 5.79; N, 8.47. Found: C, 50.62; H, 5.71; N, 8.51	65.8	38.5
3g	^{1}H NMR (D_2O, 500 MHz), δ: 7.28 (t, $J_{2',3'} = 7.8$ Hz, $J_{3',4'} = 7.8$ Hz, $J_{4',5'} = 7.8$ Hz, $J_{5',6'} = 7.8$ Hz, 2H, H-3′ and H-5′), 7.01–7.06 (m, 3H, H-2′, H-6′ and H-4′), 4.70 (m, 1H, H-5), 3.42–3.90 [m, 7H, CH(OH)CH(OH)CH(OH)CH_2OH and NCH_2], 2.88 (s, 3H, CH_3N). IR (KBr), ν: 3300 (OH), 1650 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 297 (M^+ + 1) (28), 296 (M^+) (53), 116 (46), 93 (48), 77 (20), 43 (100), 31 (43), 15 (12). Anal. Calcd. for $C_{14}H_{20}N_2O_5$ (%): C, 56.75; H, 6.80; N, 9.45. Found: C, 56.32; H, 6.84; N, 9.37	7.9	7.7
3h	^{1}H NMR (D_2O, 500 MHz), δ: 6.92 (d, $J_{2',3'} = J_{5',6'} = 8.7$ Hz, 2H, H-2′ and H-6′), 6.77 (d, $J_{2',3'} = J_{5',6'} = 8.7$ Hz, 2H, H-3′ and H-5′), 4.70 (m, 1H, H-5), 3.40–3.90 [m, 7H, CH(OH)CH(OH)CH(OH)CH_2OH and NCH_2], 2.86 (s, 3H, CH_3N). IR (KBr), ν: 3400 (OH), 1660 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 312 (M^+) (0.4), 135 (11), 109 (8), 43 (100), 31 (9), 15 (3). Anal. Calcd. for $C_{14}H_{20}N_2O_6$ (%): C, 53.84; H, 6.45; N, 8.97. Found: C, 53.71; H, 6.52; N, 9.03	89.5	100
4a	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 8.45 (m, 1H, H-6′), 7.14–7.30 (m, 5H, H-3′, H-4′, H-5′, H-6 and H-7). IR (KBr), ν: 3410 (NH), 1660 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 264 (M^+) (100), 245 (73), 122 (22), 96 (25), 95 (15), 83 (16), 75 (34). Anal. Calcd. for $C_{13}H_7F_3N_2O$: C, 59.10; H, 2.67; N, 10.60. Found: C, 59.33; H, 2.73; N, 10.79	50.0	7.7
4b	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.87 (dd, $J_{2',4'} = 5.9$ Hz, $J_{4',6'} = 5.9$ Hz, $J_{2',3'} = 9.2$ Hz, $J_{5',6'} = 9.2$ Hz, 2H, H-2′ and H-6′), 7.19 (t, $J_{2',3'} = 9.2$ Hz, $J_{3',4'} = 9.2$ Hz, $J_{4',5'} = 9.2$ Hz, $J_{5',6'} = 9.2$ Hz, 2H, H-3′ and H-5′), 7.20–7.24 (m, 2H, H-6 and H-7). IR (KBr), ν: 3420 (NH), 1700 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 264 (M^+) (100), 245 (3), 122 (12), 96 (18), 95 (13), 83 (7), 75 (11). Anal. Calcd. for $C_{13}H_7F_3N_2O$: C, 59.10; H, 2.67; N, 10.60. Found: C, 59.25; H, 2.68; N, 10.49	14.3	0
4c	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 8.15 (dd, $J_{2',4'} = 6.5$ Hz, $J_{2',6'} = 2.7$ Hz, 1H, H-2′), 7.70 (ddd, $J_{2',6'} = 2.8$ Hz, $J_{4',6'} = 3.2$ Hz, $J_{5'6'} = 9.0$ Hz, 1H, H-6′), 7.35 (t, $J_{4',5'} = 9.0$ Hz, $J_{5',6'} = 9.0$ Hz, 1H, H-5′), 7.15–7.30 (m, 2H, H-6 and H-7). IR (KBr), ν: 3420 (NH), 1700 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 301 (M^+ + 2) (6), 299 (M^+) (33), 298 (22), 297 (100), 296 (15), 262 (8), 156 (10), 130 (13), 129 (10), 109 (7). Anal. Calcd. for $C_{13}H_6ClF_3N_2O$: C, 52.28; H, 2.02; N, 9.38. Found: C, 51.73; H, 2.21; N, 9.32	17.0	0
4d	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 8.29 (td, $J_{2',6'} = 5.9$ Hz, $J_{4',6'} = 9.2$ Hz, $J_{5',6'} = 9.2$ Hz, 1H, H-6′), 7.15 (t, $J_{2',3'} = 9.2$ Hz, $J_{3',4'} = 9.2$ Hz, 1H, H-3′), 7.17–7.22 (m, 3H, H-5′, H-6, H-7). IR (KBr), ν: 3420 (NH), 1700 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 282 (M^+) (100), 263 (100), 140 (43), 114 (53), 101 (24). Anal. Calcd. for $C_{13}H_6F_4N_2O$: C, 55.33; H, 2.14; N, 9.93. Found: C, 55.38; H, 2.15; N, 9.93	32.8	7.7
4e	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 8.20 (m, 1H, H-6′), 7.30 (qd, $J_{3',5'} = 9.1$ Hz, $J_{4',5'} = 9.1$ Hz, $J_{5',6'} = 9.1$ Hz, $J_{2',5'} = 2.1$ Hz, 1H, H-5′), 7.20–7.26 (m, 2H, H-6, H-7). IR (KBr), ν: 3430 (NH), 1680 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 300 (M^+) (100), 282 (14), 281 (68), 158 (45), 132 (51), 131 (21), 119 (35), 115 (32), 88 (65), 81 (63), 64 (63). Anal. Calcd. for $C_{13}H_5F_5N_2O$: C, 52.01; H, 1.68; N, 9.33. Found: C, 52.18; H, 1.67; N, 9.31	25.7	30.8
4f	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 8.40 (dd, $J_{4',6'} = 1.5$ Hz, $J_{5',6'} = 8.0$ Hz, 1H, H-6′), 7.52 (dd, $J_{3',5'} = 1.5$ Hz, $J_{3',4'} = 8.0$ Hz, 1H, H-3′), 7.45 (td, $J_{3',5'} = 1.4$ Hz, $J_{4',5'} = 8.0$ Hz, $J_{5',6'} = 8.0$ Hz, 1H, H-5′), 7.18 (td, $J_{4',6'} = 1.5$ Hz, $J_{3',4'} = 8.0$ Hz, $J_{4',5'} = 8.0$ Hz, 1H, H-4′), 7.21–7.25 (m, 2H, H-6, H-7). IR (KBr), ν: 3400 (NH), 1600 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 282 (M^+ + 2) (33), 280 (M^+) (100), 246 (16), 245 (100), 203 (18), 202 (17), 100 (17), 75 (36), 64 (26). Anal. Calcd. for $C_{13}H_7ClF_2N_2O$: C, 55.63; H, 2.51; N, 9.88. Found: C, 55.52; H, 2.50; N, 9.96	31.6	76.9
4g	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 8.07 (t, $J_{2',6'} = 2.0$ Hz, $J_{2',4'} = 2.0$ Hz, 1H, H-2′), 7.60 (ddd, $J_{2',6'} = 2.0$ Hz, $J_{4',6'} = 0.8$ Hz, $J_{5',6'} = 8.1$ Hz, 1H, H-6′), 7.54 (t, $J_{4',5'} = 8.1$ Hz, $J_{5',6'} = 8.1$ Hz, 1H, H-5′), 7.17 (ddd, $J_{4',6'} = 0.8$ Hz, $J_{2',4'} = 2.0$ Hz, $J_{4',5'} = 8.1$ Hz, 1H, H-4′), 7.20–7.30 (m, 2H, H-6, H-7). IR (KBr), ν: 3420 (NH), 1700 cm^{-1} (C=N). MS (EI, 70 eV), *m/z* (%): 282 (M^+ + 2) (33), 280 (M^+) (100), 279 (28), 245 (13), 203 (8), 202 (7), 100 (13), 75 (35), 64 (20). Anal. Calcd. for $C_{13}H_7ClF_2N_2O$: C, 55.63; H, 2.51; N, 9.88. Found: C, 55.48; H, 2.53; N, 10.00	31.6	23.1

Table 2 (*Continued*)

Number	Spectrum data	Fungicidal activity at 100 ppm (%)	
		R. solani	*P. oryzae*
4h	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 8.49 (t, $J_{2',6'} = 8.9$ Hz, $J_{5',6'} = 8.9$ Hz, 1H, H-6′), 7.38 (m, 2H, H-3′ and H-5′), 7.14–7.25 (m, 2H, H-6 and H-7). IR (KBr), ν: 3160 (NH), 1700 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 301 (M^+ + 2) (16), 299 (M^+) (50), 298 (100), 279 (16), 263 (12), 156 (7), 130 (6). Anal. Calcd. for $C_{13}H_6ClF_3N_2O$: C, 52.28; H, 2.02; N, 9.38. Found: C, 52.03; H, 2.15; N, 9.30	31.6	23.1
4i	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.60 (d, $J_{2',3'} = 8.9$ Hz, $J_{5',6'} = 8.9$ Hz, 2H, H-6′), 6.89 (d, $J_{2',3'} = 8.9$ Hz, $J_{5',6'} = 8.9$ Hz, 2H, H-3′ and H-5′), 7.20–7.30 (m, 2H, H-6 and H-7). IR (KBr), ν: 3420 (NH), 3290 (OH), 1700 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 262 (M^+) (100). Anal. Calcd. for $C_{13}H_8F_2N_2O_2$: C, 59.55; H, 3.08; N, 10.68. Found: C, 59.64; H, 3.06; N, 10.52	52.9	6.7
5a	^{1}H NMR (D_2O, 500 MHz), δ: 6.73–7.80 (m, 5H, ArH), 2.50 (s, 3H, SCH_3). IR (KBr), ν: 3120 (NH), 1610 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 332 (M^+) (33), 285 (51), 284 (100), 204 (100), 146 (23), 128 (28), 127 (62). Anal. Calcd. for $C_{14}H_9F_5N_2S$: C, 50.60; H, 2.73; N, 8.43. Found: C, 50.42; H, 2.71; N, 8.46	100	100
5b	^{1}H NMR (D_2O, 500 MHz), δ: 7.51 (m, 1H, H-6′), 7.05–7.24 (m, 2H, H-5 and H-5′), 6.75 (m, 1H, H-6), 2.55 (s, 3H, SCH_3). IR (KBr), ν: 3160 (NH), 1570 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 350 (M^+) (10), 303 (20), 302 (39), 204 (100), 189 (44), 146 (56). Anal. Calcd. for $C_{14}H_8F_6N_2S$: C, 48.01; H, 2.30; N, 8.00. Found: C, 47.94; H, 2.46; N, 7.87	92.1	100
5c	^{1}H NMR (D_2O, 500 MHz), δ: 7.82 (m, 1H, H-6′), 7.41 (m, 1H, H-2′), 7.22 (q, $J_{3',5'} = 9.3$ Hz, $J_{4',5'} = 9.3$ Hz, $J_{5',6'} = 9.3$ Hz, 1H, H-5′), 7.10 (m, 1H, H-5), 6.80 (m, 1H, H-6), 2.50 (s, 3H, SCH_3). IR (KBr), ν: 3170 (NH), 1590 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 332 (M^+) (8), 285 (21), 284 (100), 204 (16), 145 (13), 127 (19). Anal. Calcd. for $C_{14}H_9F_5N_2S$: C, 50.60; H, 2.73; N, 8.43. Found: C, 50.71; H, 2.72; N, 8.45	77.6	100
5d	^{1}H NMR (D_2O, 500 MHz), δ: 6.99–7.92 (m, 6H, ArH), 2.51 (s, 3H, SCH_3). IR (KBr), ν: 3210 (NH), 1560 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 314 (M^+) (7), 267 (17), 266 (32), 186 (100), 171 (100), 128 (62). Anal. Calcd. for $C_{14}H_{10}F_4N_2S$: C, 53.50; H, 3.21; N, 8.91. Found: C, 53.47; H, 3.40; N, 8.87	89.5	100
5e	^{1}H NMR (D_2O, 500 MHz), δ: 7.91 (m, 1H, H-6′), 7.40 (m, 1H, H-2′), 6.93–7.01 (m, 3H, H-3, H-5 and H-6), 2.49 (s, 3H, SCH_3). IR (KBr), ν: 3160 (NH), 1580 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 314 (M^+) (10), 267 (78), 266 (100), 186 (23), 171 (15), 127 (35), 95 (26). Anal. Calcd. for $C_{14}H_{10}F_4N_2S$: C, 53.50; H, 3.21; N, 8.91. Found: C, 53.68; H, 3.21; N, 8.90	84.2	100
5f	^{1}H NMR (D_2O, 500 MHz), δ: 6.85–7.95 (m, 8H, ArH), 2.50 (s, 3H, SCH_3). IR (KBr), ν: 3210 (NH), 1590 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 278 (M^+) (14), 231 (38), 230 (29), 168 (100), 153 (53), 110 (38), 95 (26). Anal. Calcd. for $C_{14}H_{12}F_2N_2S$: C, 60.42; H, 4.35; N, 10.07. Found: C, 60.47; H, 4.27; N, 10.08	81.6	100
5g	^{1}H NMR (D_2O, 500 MHz), δ: 7.71 (m, 2H, H-2′ and H-6′), 7.05 (t, $J_{2,3} = J_{2',3'} = J_{5,6} = J_{5',6'} = 8.8$ Hz, H-3, H-5, H-3′ and H-5′), 6.90 (m, 2H, H-2′ and H-6′), 2.42 (s, 3H, SCH_3). IR (KBr), ν: 3150 (NH), 1580 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 278 (M^+) (63), 231 (58), 230 (82), 168 (100), 153 (48), 110 (79), 95 (02). Anal. Calcd. for $C_{14}H_{12}F_2N_2S$: C, 60.42; H, 4.35; N, 10.07. Found: C, 60.54; H, 4.36; N, 10.05	78.9	100
5h	^{1}H NMR (D_2O, 500 MHz), δ: 6.91–7.92 (m, 6H, ArH), 2.43 (s, 3H, SCH_3). IR (KBr), ν: 3200 (NH), 1540 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 346 (M^+) (6), 302 (13), 300 (67), 298 (100), 204 (12), 202 (35). Anal. Calcd. for $C_{14}H_{10}Cl_2F_2N_2S$: C, 48.43; H, 2.90; N, 8.07. Found: C, 48.58; H, 2.91; N, 8.10	65.8	100
5i	^{1}H NMR (D_2O, 500 MHz), δ: 7.94 (m, 1H, H-2′), 7.58 (m, 1H, H-6′), 7.19 (t, $J_{4,5} = J_{4',5'} = 9.0$ Hz, $J_{5,6} = J_{5',6'} = 9.0$ Hz, 2H-5 and H-5′), 7.01 (m, 1H, H-2), 6.85 (m, 1H, H-6), 2.43 (s, 3H, SCH_3). IR (KBr), ν: 3180 (NH), 1570 cm^{-1} (C=N). MS (EI, 70 eV), m/z (%): 346 (M^+) (2), 302 (12), 300 (66), 298 (100), 143 (15), 129 (13). Anal. Calcd. for $C_{14}H_{10}Cl_2F_2N_2S$: C, 48.43; H, 2.90; N, 8.07. Found: C, 48.62; H, 2.88; N, 8.09	38.3	92.3
6a	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.20 (td, $J_{4',6'} = 9.1$ Hz, $J_{5',6'} = 9.1$ Hz, $J_{2',6'} = 5.6$ Hz, 1H, H-6′), 6.96 (ddd, $J_{2',3'} = 8.7$ Hz, $J_{3',4'} = 11.2$ Hz, $J_{3',5'} = 2.8$ Hz, 1H, H-3′), 6.85 (tdd, $J_{2',5'} = 1.5$ Hz, $J_{3',5'} = 2.8$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-5′), 4.50 (d, $J_{1,2} = 8.0$ Hz, 1H, H-1), 3.76 (dd, $J_{5,6} = 2.2$ Hz, $J_{gem} = 12.3$ Hz, 1H, H-6a), 3.58 (dd, $J_{5,6} = 5.5$ Hz, $J_{gem} = 12.3$ Hz, 1H, H-6b), 3.41 (m, 2H, H-2 and H-3), 3.20 (m, 2H, H-4 and H-5). IR (KBr), ν: 3310 (NH), 3250 (OH), 1600 and 1570 cm^{-1} (Ph). MS (EI, 70 eV), m/z (%): 291 (M^+) (2), 129 (100), 109 (24), 101 (73), 82 (47). Anal. Calcd. for $C_{12}H_{15}F_2NO_5 \cdot H_2O$: C, 46.60; H, 5.54; N, 4.53. Found: C, 46.54; H, 5.56; N, 4.55	0 (in vivo)	-

Table 2 (*Continued*)

Number	Spectrum data	Fungicidal activity at 100 ppm (%)	
		R. solani	*P. oryzae*
6b	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.02 (q, $J_{3',5'} = 9.1$ Hz, $J_{4',5'} = 9.1$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-5′), 6.65 (ddd, $J_{2',3'} = 12.9$ Hz, $J_{2',4'} = 6.9$ Hz, $J_{2',6'} = 2.7$ Hz, 1H, H-2′), 6.49 (d, $J_{5',6'} = 9.0$ Hz, 1H, H-6′), 4.57 (d, $J_{1,2} = 8.8$ Hz, 1H, H-1), 3.78 (dd, $J_{5,6} = 2.2$ Hz, $J_{gem} = 12.3$ Hz, 1H, H-6a), 3.62 (dd, $J_{5,6} = 5.5$ Hz, $J_{gem} = 12.3$ Hz, 1H, H-6b), 3.45 (m, 2H, H-2 and H-3), 3.35 (m, 2H, H-4 and H-5). IR (KBr), ν: 3350 (NH), 3260 (OH), 1600 cm^{-1} (Ph). MS (EI, 70 eV), *m/z* (%): 291 (M^+) (5), 142 (100), 129 (42), 113 (40). Anal. Calcd. for $C_{12}H_{15}F_2NO_5 \cdot H_2O$: C, 46.60; H, 5.54; N, 4.53. Found: C, 46.58; H, 5.52; N, 4.56	90	–
6c	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 6.92 (t, $J_{2',3'} = 8.9$ Hz, $J_{2',4'} = 8.9$ Hz, $J_{4'6'} = 8.9$ Hz, $J_{5',6'} = 8.9$ Hz, 2H, H-3′ and H-5′), 6.71 (q, $J_{2',3'} = 8.9$ Hz, $J_{2',4'} = 4.5$ Hz, $J_{4'6'} = 4.5$ Hz, $J_{5',6'} = 8.9$ Hz, 2H, H-2′ and H-6′), 4.60 (d, $J_{1,2} = 8.8$ Hz, 1H, H-1), 3.79 (dd, $J_{5,6} = 2.0$ Hz, $J_{gem} = 12.3$ Hz, 1H, H-6a), 3.58 (dd, $J_{5,6}$ =5.6 Hz, $J_{gem} = 12.3$ Hz, 1H, H-6b), 3.41 (m, 2H, H-2 and H-3), 3.20 (m, 2H, H-4 and H-5). IR (KBr), ν: 3320 (NH), 3260 (OH), 1510 cm^{-1} (Ph). EIMS: *m/z* (%): 273 (M^+) (8), 124 (100), 111 (71), 95 (48), 75 (24). Anal. Calcd. for C, 49.48; H, 6.23; N, 4.81. Found: C, 49.32; H, 6.24; N, 4.81	0	–
6d	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 6.88 (qd, $J_{3',5'} = 9.0$ Hz, $J_{4',5'} = 9.0$ Hz, $J_{5',6'} = 9.0$ Hz, $J_{2',5'} = 2.1$ Hz, 1H, H-5′), 6.64 (tq, $J_{2',6'} = 4.7$ Hz, $J_{3',6'} = 2.2$ Hz, $J_{4'6'} = 9.0$ Hz, $J_{5',6'} = 9.0$ Hz, 1H, H-6′), 4.60 (d, $J_{1,2} = 8.7$ Hz, 1H, H-1), 3.79 (dd, $J_{5,6} = 2.1$ Hz, $J_{gem} = 12.4$ Hz, 1H, H-6a), 3.58 (dd, $J_{5,6} = 5.5$ Hz, $J_{gem} = 12.4$ Hz, 1H, H-6b), 3.45 (m, 2H, H-2 and H-3), 3.38 (m, 2H, H-4 and H-5). IR (KBr), ν: 3310 (NH), 3260 (OH), 1590 and 1570 (Ph) m^{-1}. MS (EI, 70 eV), *m/z* (%): 309 (M^+) (3), 147 (100), 119 (47). Anal. Calcd. for $C_{12}H_{14}F_3NO_5 \cdot H_2O$: C, 44.04; H, 4.93; N, 4.28. Found: C, 43.90; H, 4.90; N, 4.28	0	–
6e	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.05 (t, $J_{4',5'} = 8.9$ Hz, $J_{5',6'} = 8.9$ Hz, 1H, H-5′), 6.85 (s, 1H, H-2′), 6.67 (dd, $J_{4',6'} = 6.1$ Hz, $J_{5',6'} = 8.9$ Hz, 1H, H-6′), 4.58 (d, $J_{1,2} = 8.2$ Hz, 1H, H-1), 3.76 (dd, $J_{5,6} = 2.2$ Hz, $J_{gem} = 12.3$ Hz, 1H, H-6a), 3.62 (dd, $J_{5,6} = 5.5$ Hz, $J_{gem} = 12.3$ Hz, 1H, H-6b), 3.45 (m, 2H, H-2 and H-3), 3.35 (m, 2H, H-4 and H-5). IR (KBr), ν: 3310 (NH), 3250 (OH), 1600 and 1500 cm^{-1} (Ph). MS (EI, 70 eV), *m/z* (%): 309 ($M^+ + 2$) (33), 307 (M^+) (100), 290 (5), 288 (15), 160 (8), 158 (24). Anal. Calcd. for $C_{12}H_{15}ClFNO_5 \cdot H_2O$: C, 44.25; H, 5.26; N, 4.30. Found: C, 44.18; H, 5.24; N, 4.32	70	–
6f	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.10 (q, $J_{3',5'} = 9.2$ Hz, $J_{4',5'} = 9.2$ Hz, $J_{5',6'} = 9.2$ Hz, 1H, H-5′), 6.76 (ddd, $J_{2',3'} = 12.8$ Hz, $J_{2',4'} = 6.8$ Hz, $J_{2',6'} = 2.5$ Hz, 1H, H-2′), 6.61 (m, 1H, H-6′), 4.63 (d, $J_{1,2} = 8.8$ Hz, 1H, H-1), 4.00 (d, $J_{5,6} = 2.0$ Hz, 1H, H-6a), 3.80 (t, $J_{3,4} = 6.1$ Hz, $J_{4,5} = 6.1$ Hz, 1H, H-4), 3.63–3.75 (m, 4H, H-2, H-3, H-5 and H-6b). IR (KBr), ν: 3340 (NH), 3250 (OH), 1595 cm^{-1} (Ph). MS (EI, 70 eV), *m/z* (%): 291 (M^+) (5), 143 (19), 142 (100), 129 (30), 115 (23), 113 (25). Anal. Calcd. for $C_{12}H_{15}F_2NO_5$: C, 49.49; H, 5.19; N, 4.86. Found: C, 48.91; H, 5.12; N, 4.74	0	–
6g	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.11 (q, $J_{3',5'} = 9.0$ Hz, $J_{4',5'} = 9.0$ Hz, $J_{5',6'} = 9.0$ Hz, 1H, H-5′), 6.78 (ddd, $J_{2',3'} = 12.9$ Hz, $J_{2',4'} = 6.8$ Hz, $J_{2',6'} = 2.7$ Hz, 1H, H-2′), 6.61 (m, 1H, H-6′), 4.93 (d, $J_{1,2} = 2.1$ Hz, 1H, H-1), 4.03 (d, $J_{5,6} = 2.7$ Hz, 1H, H-6a), 3.88 (dd, $J_{5,6} = 2.2$ Hz, $J_{gem} = 12.2$ Hz, 1H, H-6b), 3.70–3.74 (m, 2H, H-2 and H-3), 3.63 (t, $J_{3,4} = 9.7$ Hz, $J_{4,5} = 9.7$ Hz, 1H, H-4), 3.49 (m, 1H, H-5). IR (KBr), ν: 3345 (NH), 3270 (OH), 1602 cm^{-1} (Ph). MS (EI, 70 eV), *m/z* (%): 291 (M^+) (2), 143 (11), 142 (100), 129 (43), 114 (26), 113 (24). Anal. Calcd. for $C_{12}H_{15}F_2NO_5$: C, 49.11; H, 5.09; N, 4.78. Found: C, 48.91; H, 5.12; N, 4.74	0	–
6h	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 6.94 (q, $J_{3',5'} = 9.1$ Hz, $J_{4',5'} = 9.1$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-5′), 6.57 (ddd, $J_{2',3'} = 12.9$ Hz, $J_{2',4'} = 6.9$ Hz, $J_{2',6'} = 2.7$ Hz, 1H, H-2′), 6.41 (m, 1H, H-6′), 4.45 (d, $J_{1,2} = 8.7$ Hz, 1H, H-1), 3.72 (dd, $J_{4,5} = 5.38$ Hz, $J_{gem} = 11.4$ Hz, 1H, H-5a), 3.45 (m, 1H, H-4), 3.34 (t, $J_{2,3} = 9.1$ Hz, $J_{3,4} = 9.1$ Hz, 1H, H-3), 3.20–3.26 (m, 2H, H-2 and H-5b). IR (KBr), ν: 3320 (NH), 3270 (OH), 1580 cm^{-1} (Ph). MS (EI, 70 eV), *m/z* (%): 261 (M^+) (4), 260 ($M^+ - 1$) (26), 130 (13), 129 (100), 114 (18), 113 (23). Anal. Calcd. for $C_{11}H_{13}F_2NO_4$: C, 50.58; H, 5.02; N, 5.36. Found: C, 50.32; H, 5.03; N, 5.38	0	–
6i	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.11 (t, $J_{4',5'} = 9.1$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-5′), 6.97 (dd, $J_{2',6'} = 2.7$ Hz, $J_{2',4'} = 6.2$ Hz, 1H, H-2′), 6.77 (ddd, $J_{2',6'} = 2.7$ Hz, $J_{4'6'} = 5.4$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-6′), 4.62 (d, $J_{1,2} = 8.7$ Hz, 1H, H-1), 4.00 (d, $J_{5,6} = 2.2$ Hz, 1H, H-6a), 3.80 (t, $J_{3,4} = 6.2$ Hz, $J_{4,5} = 6.2$ Hz, 1H, H-4), 3.72–3.77 (m, 3H, H-3, H-5 and H-6b), 3.64 (t, $J_{1,2} = 8.7$ Hz, $J_{2,3} = 8.7$ Hz, 1H, H-2). IR (KBr), ν: 3340 (NH), 3260 (OH), 1595 and 1500 cm^{-1} (Ph). MS (EI, 70 eV), *m/z* (%): 309 ($M^+ + 2$) (3), 307 (M^+) (5), 160 (35), 158 (100), 147 (9), 145 (27), 131 (7), 129 (15). Anal. Calcd. for $C_{12}H_{15}ClFNO_5$: C, 46.84; H, 4.91; N, 4.55. Found: C, 46.47; H, 4.84; N, 4.49	0	–
6j	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.02 (t, $J_{4',5'} = 8.9$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-5′), 6.98 (dd, $J_{2',6'} = 2.6$ Hz, $J_{2',4'} = 6.2$ Hz, 1H, H-2′), 6.79 (m, 1H, H-6′), 4.94 (d, $J_{1,2} = 2.1$ Hz, 1H, H-1), 4.03 (d, $J_{5,6} = 3.1$ Hz, 1H, H-6a), 3.89 (dd, $J_{5,6} = 1.7$ Hz, $J_{gem} = 12.3$ Hz, 1H, H-6b), 3.69–3.78 (m, 2H, H-2 and H-3), 3.63 (t, $J_{3,4} = 9.7$ Hz, $J_{4,5} = 9.7$ Hz, 1H, H-4), 3.48 (m, 1H, H-5). IR (KBr), ν: 3320 (NH), 3250 (OH), 1600 and 1500 cm^{-1} (Ph). MS (EI, 70 eV), *m/z* (%): 309 ($M^+ + 2$) (9), 307 (M^+) (23), 160 (32), 158 (100), 147 (17), 145 (53), 131 (9), 129 (20). Anal. Calcd. for $C_{12}H_{15}ClFNO_5$: C, 46.84; H, 4.91; N, 4.55. Found: C, 46.75; H, 4.93; N, 4.50	0	–

Table 2 (*Continued*)

Number	Spectrum data	Fungicidal activity at 100 ppm (%)	
		R. solani	*P. oryzae*
6k	^{1}H NMR (CD_3COCD_3, 500 MHz), δ: 7.12 (t, $J_{4',5'} = 9.1$ Hz, $J_{5',6'} = 9.1$ Hz, 1H, H-5′), 6.95 (dd, $J_{2',6'} = 2.5$ Hz, $J_{2',4'} = 6.1$ Hz, 1H, H-2′), 6.76 (m, 1H, H-6′), 4.63 (d, $J_{1,2} = 8.7$ Hz, 1H, H-1), 3.72 (dd, $J_{4,5} = 5.3$ Hz, $J_{gem} = 11.4$ Hz, 1H, H-5a), 3.63 (m, 1H, H-4), 3.52 (t, $J_{1,2} = 9.1$ Hz, $J_{2,3} = 9.1$ Hz, 1H, H-3), 3.38–3.44 (m, 2H, H-2 and H-5b). IR (KBr), ν: 3320 (NH), 3260 (OH), 1585 and 1500 cm^{-1} (Ph). MS (EI, 70 eV), m/z (%): 279 ($M^+ + 2$) (3), 278 ($M^+ + 1$) (10), 277 (M^+) (8), 276 ($M^+ - 1$) (28), 160 (31), 158 (100), 147 (22), 145 (68), 131 (9), 129 (21). Anal. Calcd. for $C_{11}H_{13}ClFNO_4$: C, 47.58; H, 4.72; N, 5.04. Found: N, 47.39; H, 4.71; N, 5.02	0	–

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 fluorophenyl isothiocyanate

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

3.2. Synthetic procedure for substituted thiourea

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 to the next reaction directly.

3.3. General synthetic procedure for substituted phenylimino-thiazolidine (*1*)

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.

3.4. General synthetic procedure for substituted phenylimino-oxazolidine (*2*)

Substituted thiourea (0.01 mol) was dissolved in CH_3COCH_3/Et_2O (1:6 v/v, 30 ml). To the reaction mixture was added in batch yellow HgO (15 g, 0.07 mol). After 24 h, the resulting mixture was filtered through silica gel, and the filtrate was concentrated under reduced pressure to give the crude products, which were purified on TLC plates to give the desired products.

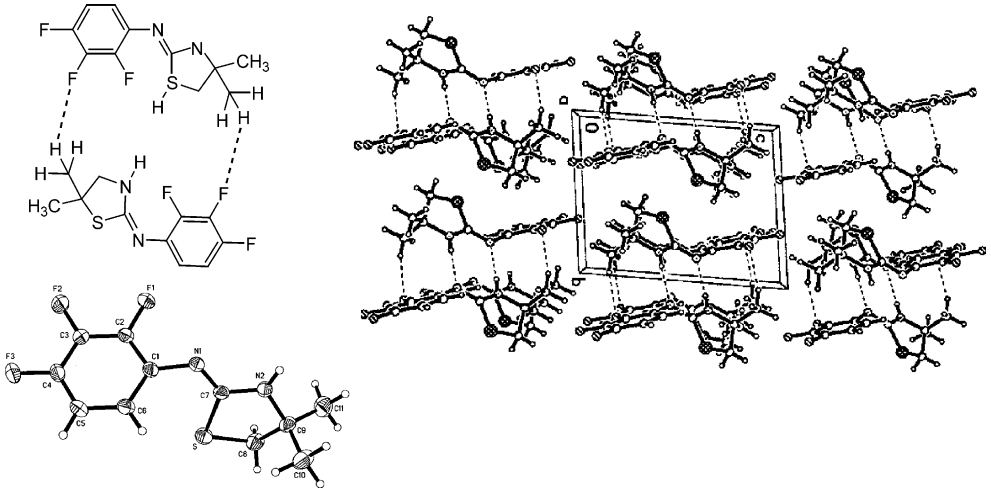
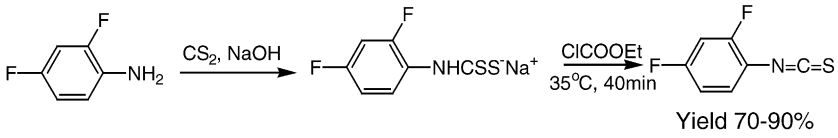


Fig. 2. The molecular structure, X-ray crystal structure and stacking spectrum of trifluorophenyl dimethylthiazolidine (**1k**).



Scheme 6.

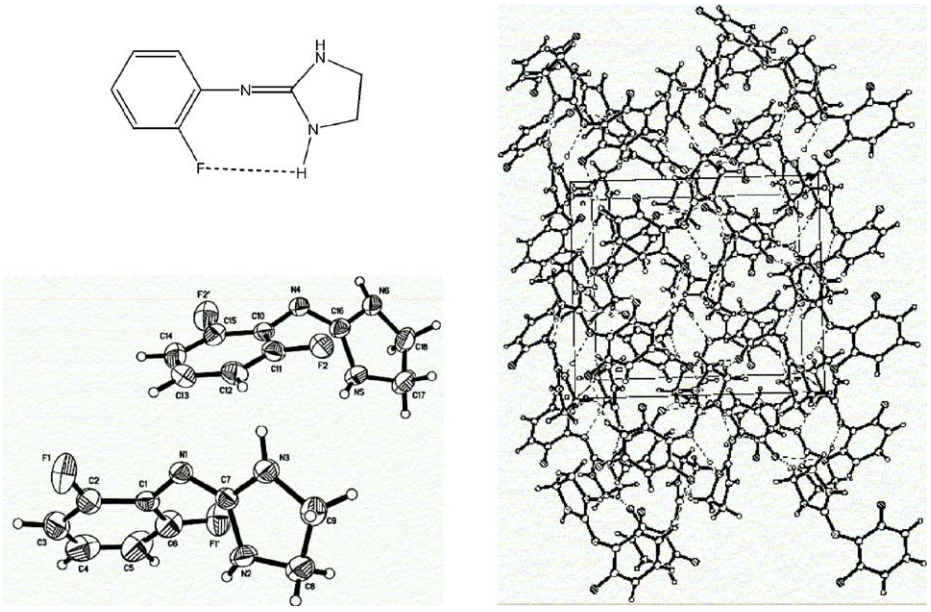


Fig. 3. The molecular structure, X-ray crystal structure and stacking spectrum of *o*-fluorophenylimino-thiazolidine.

*3.5. General synthetic procedure for substituted phenylimino-oxazolidine (**3**) and (**4**)*

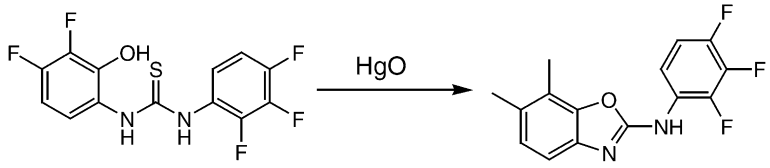
Substituted thiourea (0.01 mol), 30 ml CH_3COCH_3, 30 ml CH_3OH were added in 100 ml flask. To the reaction mixture was added in batch yellow HgO (21.6 g, 0.10 mol). After 24 h, the resulting mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude products, which was recrystallized from ethanol to give the desired products.

*3.6. General synthetic procedure for N,N′-fluorosubstituted diphenylthioureas (the intermediates of compound **5**)*

To a solution of the fluorine-containing aniline (0.01 mol) in 50 ml of ethanol was added dropwise the aryl isothiocyanate (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.

*3.7. General synthetic procedure for fluorine-containing N,N′-diphenylcarbamidothioates (**5**)*

To a solution of the above thiourea (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 (4:10 v/v) to give a white solid.



Scheme 7.

3.8. General synthetic procedure for compound (**6**)

To a mixture of fluoro-substituted aniline (0.01 mol), D-glucose (0.01 mol) and water (8 ml) was added 1 ml of a 6% HCl solution. The mixture was kept for 10 min at 60 °C and then cooled to 0 °C. The resulting mass was filtered, washed with 2 ml water, dried and recrystallized from C_2H_5OH to give white solids.

4. Conclusion

Based on the structural features of trehazolin, six series of compounds were designed and synthesized. Some facile and convenient synthetic methods were obtained for the synthesis of fluorine-containing arylisothiocyanate and fluorophenyl aminobenzoxazoles, respectively. X-ray crystal analysis suggested the presence of novel intermolecular (aromatic $CH_3 \cdots FCsp^2$) and intramolecular ($NH \cdots FCsp^2$) hydrogen bonds with fluorine as an acceptor. Bio-screening showed that some of compounds had significant fungicidal activity to *R. solani* and *P. oryzae* in vitro at 100 ppm or good bioactivity at 1000 ppm in vivo.

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