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Synthesis, characterization and fungicidal activities of novel fluorinated 3,5-disubstituted-4*H*-1,2,4-triazol-4-amines

Min Chen [a,b], Xian-Feng Wang [a,b], Si-Si Wang [b,c], Yi-Xiao Feng [c], Feng Chen [c], Chun-Long Yang [a,b,c,*]

[a] *Key Laboratory of Monitoring and Management of Crop Diseases and Pest Insects, Ministry of Agriculture, Nanjing Agricultural University, Nanjing 210095, PR China*
[b] *Jiangsu Key Laboratory of Pesticide Science, Nanjing Agricultural University, Nanjing 210095, PR China*
[c] *Department of Chemistry, College of Science, Nanjing Agricultural University, Nanjing 210095, PR China*

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ABSTRACT

Thiocarbohydrazide and substituted benzoyl hydrazine were used as starting materials to synthesize fifteen fluorinated 3,5-disubstituted-4*H*-1,2,4-triazol-4-amines. All the title compounds were characterized using IR, ^{1}H and ^{19}F NMR spectroscopy, mass spectrometry (MS) and elemental analysis. The structures of compounds **6g** and **7** were confirmed by X-ray diffraction crystallography. The preliminary bioassay results showed that these compounds exhibited certain fungicidal activities against *Rhizoctonia solani*, *Fusarium graminearum*, *Botrytis cinerea* and *Colletotrichum capsici* at the concentration of 100 μg/mL.

1. Introduction

1,2,4-Triazole fungicides, which inhibit the biosynthesis of ergosterin in fungi, show strong fungicidal activities, broad fungicidal spectrum and excellent inner absorption properties. Fluorine as a unique atom can modulate the physical properties of a molecule, and the fungicidal activities were often enhanced by introducing fluorine into triazole derivatives [1–4]. Flusilazole, fluotrimazole, epoxiconazole and flutriafol, which are successful examples of fluorinated 1,2,4-triazole fungicides, have been widely used in plant protecting [5,6].

In recent years, 1,2,4-triazol-4-amine and its many derivatives have been synthesized, some of them were found to present notable fungicidal activities [7–11]. But most of these 1,2,4-triazol-4-amine derivatives have not shown practical application value in plant pathogen control, because their bioactivities were not high enough. In this article, a single fluorine atom and the trifluoromethyl group were introduced at the 5-position of 1,2,4-triazol-4-amine respectively to synthesize fluorinated 3,5-disubstituted-4*H*-1,2,4-triazol-4-amine derivatives, with a view to reveal the influence of fluorine on the fungicidal activities of 1,2,4-triazol-4-amines.

2. Results and discussion

2.1. Chemistry

The synthetic routes for the target compounds are illustrated in Schemes 1 and 2. The intermediate 4-amino-5-(trifluoromethyl)-4*H*-1,2,4-triazole-3-thiol (**2**) was prepared by the reaction of trifluoroacetic acid (TFA) with thiocarbohydrazide (TCH, **1**) in refluxing water for 5 h according to the reported method [12–18].

The intermediates 4-amino-5-(4-fluorophenyl)-4*H*-1,2,4-triazole-3-thiol (**5a**) and 4-amino-5-(4-(trifluoromethyl)phenyl)-4*H*-1,2,4-triazole-3-thiol (**5b**) were synthesized from 4-fluorobenzoyl hydrazine (**3a**) and 4-(trifluoromethyl)benzoyl hydrazine (**3b**) *via* a facile two-step procedure including salt formation and cyclization according to the reported method [17–20].

The synthesis of the target compounds **6a–i** were performed by the alkylation of **2**, **5a–b** with three different alkyl bromide in aqueous solution in the presence of NaOH as a base (Scheme 1). 3-(Methylthio)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-4-amine (**6j**) was synthesized by alkylation of intermediate **2** with iodomethane. Then, **6j** was oxidized by 30% H_2O_2 aqueous solution in acetic acid to give 3-(methylsulfonyl)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-4-amine (**7**) [21,22]. The reaction of **7** with *p*-nitropenol in refluxing anhydrous toluene afforded 3-(4-nitrophenoxy)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-4-amine (**8**) in 28% yield (Scheme 2) [23,24].

* Corresponding author at: Key Laboratory of Monitoring and Management of Crop Diseases and Pest Insects, Ministry of Agriculture, Nanjing Agricultural University, Nanjing 210095, PR China.
E-mail address: chunlongyang@yahoo.com.cn (C.-L. Yang).

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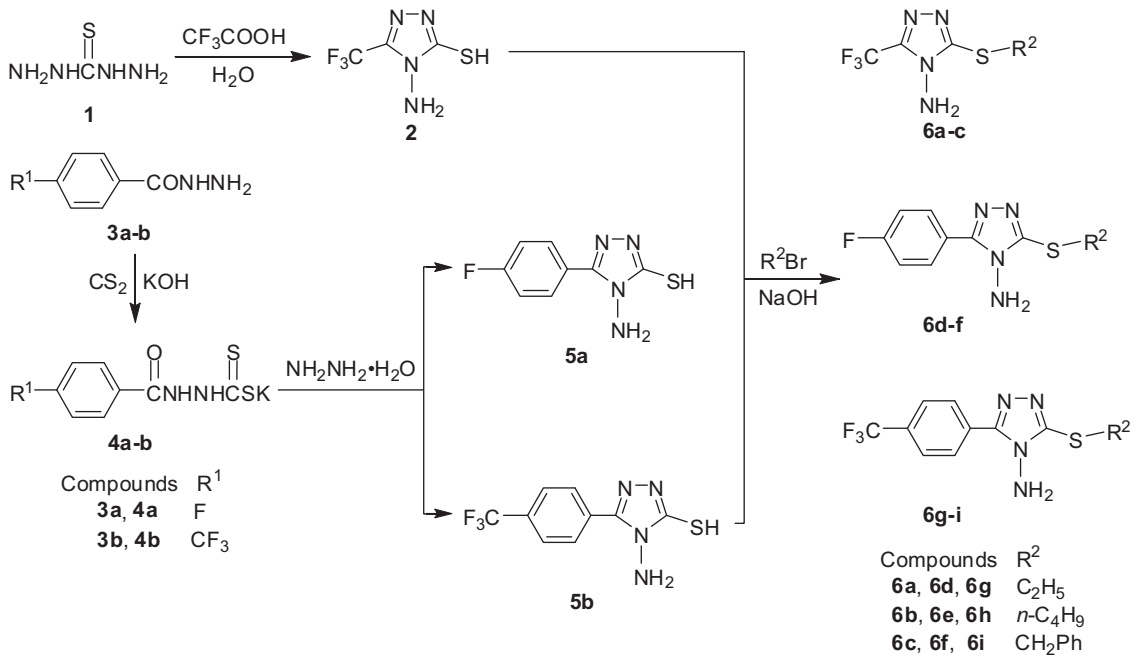


Scheme 1. Synthesis of some 3,5-disubstituted-4*H*-1,2,4-triazol-4-amines.

2.2. Structure

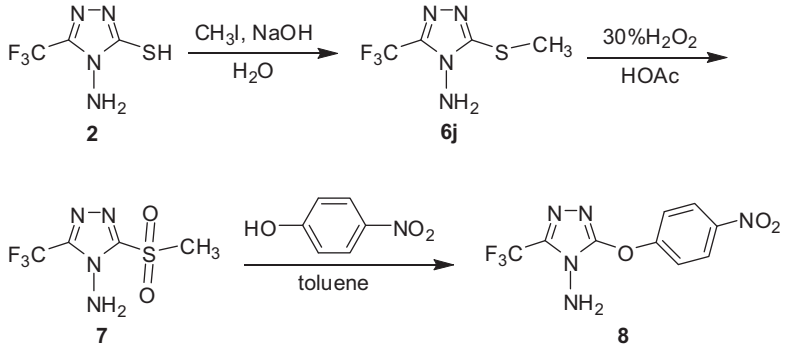
The IR spectrum of the target compounds showed the peaks at 3368–3126 cm^{-1} due to the N–H stretching vibration of amino-group at the 4-postion of 1,2,4-triazole. The broad and strong absorption peaks at 1329–1110 cm^{-1} were assigned to the C–F stretching vibration. The strong peaks at 1337 cm^{-1} and 1157 cm^{-1} of compound **7** could be attributed to asymmetric and symmetric stretching vibration of the sulfone, respectively.

The ^1H NMR spectrum of the target compounds showed signals at δ 4.33–5.78 ppm for the protons of NH_2 at the 4-postion of 1,2,4-triazole. The signal for the protons of CH_3 in **7** appeared at the low field, δ 3.61 ppm, due to the influence of the sulfone. The peaks between δ 4.26–4.38 ppm were corresponding to the protons of CH_2 of the benzyl group at the 3-position of compounds **6c**, **6f** and **6i**. The signals for the proton of SH at the 3-position of compounds **2** and **5a**–**b** were found between δ 10.86–13.95 ppm. The ^{19}F NMR spectrum showed peaks at δ −63.42 to −66.24 ppm for compounds **2**, **5b**, **6a**–**c**, **6g**–**j**, **7** and **8**, and at δ −107.33 to −110.66 ppm for compounds **5a** and **6d**–**f**.

Moreover, all the target compounds showed parent ion [M^+] peaks in their MS spectra. All the elemental analysis data matched their molecular formulas.

2.3. X-ray crystal structures of compounds 6g and 7

In the crystal structure of 3-(ethylthio)-5-(4-(trifluoromethyl)-phenyl)-4*H*-1,2,4-triazol-4-amine (**6g**) (Fig. 1), the intramolecular hydrogen bond C(8)–H(8)···N(1) (Table 1), together with the atoms C(3), C(2) and N(2), formed a new six-membered ring. The trifluoromethyl group connecting to the benzene ring appeared in a disordered state. Due to the strong electron withdrawing effect of trifluoromethyl group, the bond length of C(6)–C(9) [1.496(2) Å] was shorter than the normal length of C–C single bond (1.53 Å). The bond lengths of S(1)–C(1) [1.7401(16) Å], C(2)–C(3) [1.471(2) Å] and N(1)–N(2) [1.4051(19) Å] were shorter than their normal bond lengths because of the presence of an electronic delocalization. The bond C(2)–C(3) connected the benzene ring to the triazole ring to form a large conjugated system. In the packing diagram of the compound **6g** (Fig. 2), the molecules connected each other through intermolecular hydrogen bonds N(1)–H(1A)···N(3) and N(1)–H(1B)···S(1) (Table 1). There were $\pi\cdots\pi$ stacking interactions between the approximately parallel triazole rings. The dihedral angle was 12.094(38)°. The centroid–centroid and centroid-to-plane distances were 3.4612(3) Å and 3.3841(14) Å, respectively. Moreover, there were intermolecular C–H···π (d(H···π), 3.0914(3) Å; d(C···π), 3.7766(17) Å; ∠(C–H···π), 131.930(105)°) interactions of C(7)–H(7) to the benzene ring.



Scheme 2. Synthesis of 3-(4-nitrophenoxy)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-4-amine.

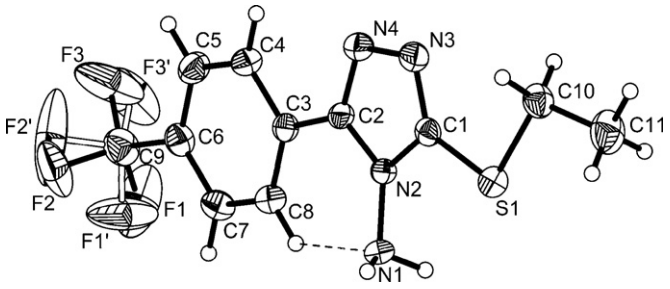


Fig. 1. ORTEP diagram of compound **6g**.

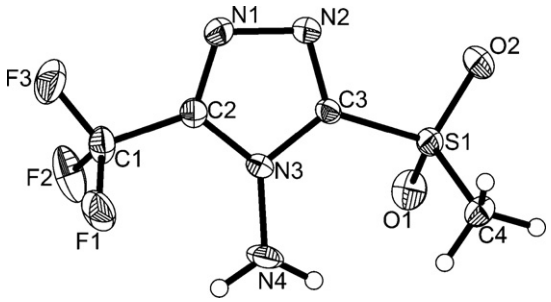


Fig. 3. ORTEP diagram of compound **7**.

Table 1
Hydrogen bonds geometry of compounds **6g** and **7** (Å,°).

Compd.	D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	∠(DHA)
6g	N(1)–H(1A)···N(3)[a]	0.92(2)	2.12(2)	3.036(2)	175.3(16)
	N(1)–H(1B)···S(1)[b]	0.88(2)	2.68(2)	3.3927(16)	138.5(18)
	C(8)–H(8)···N(1)	0.93	2.37	3.021(2)	127
7	N(4)–H(4D)···N(4)[a]	0.86	2.60	3.044(3)	113.6
	N(4)–H(4E)···O(1)[a]	0.86	2.42	3.117(3)	138.6
	C(4)–H(4A)···O(2)[b]	0.96	2.548	3.426(3)	152
	C(4)–H(4B)···F(1)[c]	0.96	2.462	3.286(3)	144
	C(4)–H(4C)···O(2)[d]	0.96	2.485	3.342(3)	149

Symmetry code: for the compound **6g**: (a) $-x$, $1/2+y$, $1/2-z$, (b) x, $1/2-y$, $1/2+z$; for the compound **7**: (a) $1-x$, $1-y$, $2-z$, (b) x, $1+y$, z, (c) $1/2-x$, $-1/2+y$, $3/2-z$, (d) $3/2-x$, $1/2+y$, $3/2-z$.

The bond lengths of the sulfone group in compound **7** (Fig. 3) were 1.4337(16) Å (S(1)–O(1)) and 1.4350(19) Å (S(1)–O(2)), accordant with the normal length (1.43 Å). There were as many as five intermolecular hydrogen bonds, N(4)–H(4E)···O(1), C(4)–H(4A)···O(2), C(4)–H(4 C)···O(2), N(4)–H(4D)···N(4) and C(4)–H(4B)···F(1), between the neighboring molecules. They jointly constituted a stable 3-D supramolecular network structure with many cavities (Fig. 4).

2.4. Fungicidal activities

The screening results of *in vitro* fungicidal activities of compounds **2**, **5a–b**, **6a–j**, **7** and **8** at the concentration of 100 μg/mL are summarized in Table 2. The fungicide propiconazole was used as a control drug. Compounds **5a–b**, **6e–i** and **8** showed observable fungicidal activities of more than 50% against *Rhizoctonia solani*. Among them, compounds **5b** and **6g** exhibited the highest activities with inhibitory rates of 74.9% and 72.2%, respectively. Against *Fusarium graminearum*, *Botrytis cinerea* and *Colletotrichum capsici*, all the title compounds showed low fungicidal activities with the inhibitory rates of less than 50%, except for compound **5b** which exhibited notable inhibitory rates of 77.5% against *B. cinerea* and 67.9% against *C. capsici*, and compound **8** showed a medium inhibitory rate of 51.9% against *C. capsici*.

By the preliminary structure–activity relationship analysis, it was concluded that compounds **5a–b** and **6d–i** had better fungicidal activities than compounds **2** and **6a–b**. And this could be due to the introducing of the fluorinated benzenes. Especially, when the connection mode of trifluoromethyl group at the 5-position of 1,2,4-triazole was changed from directly to indirectly *via* a phenyl group, the corresponding compounds' fungicidal activities obviously were enhanced. Meanwhile, compound **8** had better fungicidal activities than compounds **6j** and **7**, and compound **6c** had better fungicidal activities than compounds **2**, **6a** and **6b**, which meant that introducing the phenyl group at the 3-position of 1,2,4-triazole could also improve the fungicidal activities when the trifluoromethyl group was connected directly at the 5-position of 1,2,4-triazole.

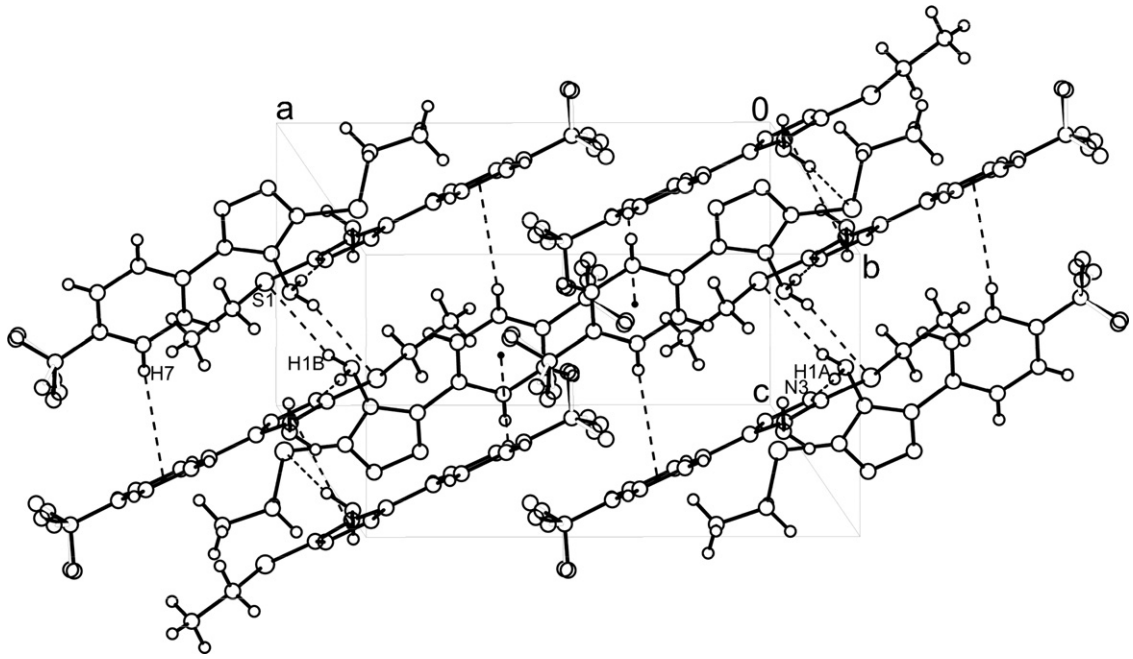


Fig. 2. Crystal packing diagram of compound **6g** showing the intermolecular interactions.

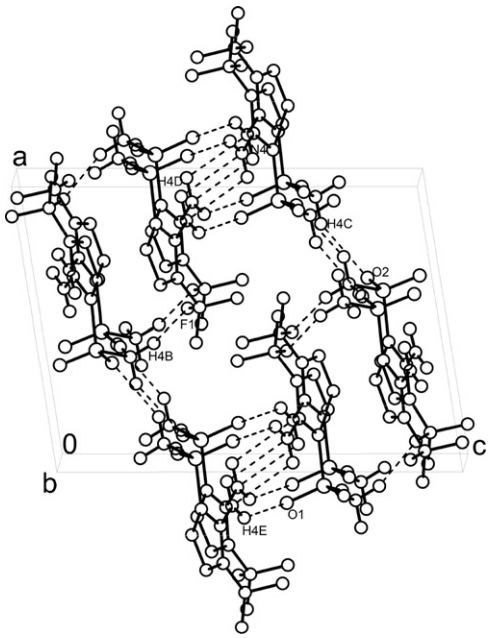


Fig. 4. Crystal packing diagram of compound **7** showing the intermolecular interactions.

Table 2
Fungicidal activities of compounds **2**, **5a–b**, **6a–j**, **7** and **8** (100 μg/mL, inhibitory rate percent).

Compd.	Inhibitory rate [a] (%)			
	R. solani	*F. graminearum*	*B. cinerea*	*C. capsici*
2	24.4 ± 3.5	3.2 ± 1.4	−0.3 ± 2.5	7.1 ± 3.6
5a	63.2 ± 4.0	23.7 ± 1.7	42.1 ± 6.2	26.5 ± 3.9
5b	74.9 ± 0.8	37.9 ± 4.4	77.5 ± 2.5	67.9 ± 5.3
6a	23.0 ± 9.7	−0.5 ± 3.2	0.0 ± 2.7	9.6 ± 1.2
6b	18.4 ± 6.4	2.2 ± 1.7	9.2 ± 4.3	6.0 ± 2.2
6c	42.8 ± 14.6	19.6 ± 3.0	18.2 ± 3.4	18.7 ± 1.1
6d	19.9 ± 9.2	13.2 ± 4.4	9.9 ± 2.2	6.2 ± 1.0
6e	51.7 ± 4.3	21.2 ± 1.6	18.4 ± 5.4	46.0 ± 2.2
6f	68.2 ± 6.6	21.8 ± 1.3	13.7 ± 4.3	18.7 ± 7.0
6g	72.2 ± 2.3	23.9 ± 1.9	27.6 ± 3.1	24.7 ± 1.1
6h	53.3 ± 10.5	13.2 ± 3.1	5.9 ± 2.6	16.2 ± 7.5
6i	50.2 ± 5.9	16.4 ± 2.4	7.4 ± 4.0	12.2 ± 0.7
6j	12.9 ± 3.0	−0.8 ± 2.8	3.7 ± 3.7	1.7 ± 1.6
7	42.6 ± 3.6	15.5 ± 0.9	11.2 ± 2.3	5.4 ± 0.7
8	51.2 ± 5.2	27.7 ± 1.6	36.6 ± 3.2	51.9 ± 2.2
Propiconazole	100.0	95.4 ± 0.7	100.0	100.0

[a] The values are expressed as means ± SD of three replicates.

3. Conclusions

In summary, fluorine was introduced to the 5-position of 1,2,4-triazole to design and synthesize fifteen fluorinated 3,5-disubstituted-4*H*-1,2,4-triazol-4-amines. The structures of these compounds were well supported by spectroscopic data, elemental analysis and single crystal X-ray diffraction analysis. The antifungal bioassay results demonstrated that the title compounds showed different fungicidal activities at the concentration of 100 μg/mL. Compound **5b** was the best with inhibitory rates of 74.9%, 77.5% and 67.9% against *R. solani*, *B. cinerea* and *C. capsici*, respectively. The structure–activity relationship analysis revealed that introducing the fluorinated phenyl, especially the 4-trifluoromethyl phenyl group, at the 5-position of 1,2,4-triazol-4-amine, or introducing a phenyl group at the 3-position while the trifluoromethyl group was connected at the 5-position directly were helpful to improve the fungicidal activities.

4. Experimental

4.1. General procedures

The melting points of the products were determined on a WRS-1B digital melting-point apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet 380 FT-IR spectrometer with KBr pellets in the range of 4000–400 cm^{-1}. ^1H and ^{19}F NMR spectra were taken on a Bruker AV spectrometer at 400 and 376 MHz with $CDCl_3$ or DMSO-d_6 as the solvent. The chemical shifts are reported in ppm relative to the appropriate standards, TMS for ^1H and $CFCl_3$ for ^{19}F. Mass spectra were recorded on a GC/MS-QP2010 spectrometer using a direct injection technique. The elemental analyses were performed on an Elementar Vario EL III element analyzer. The X-ray diffraction was performed with a Brucker Smart APEX II CCD diffractometer. A suitable crystal for compound **6g** was grown in absolute ethanol and for compound **7** the crystal was grown in water. All the reagents were analytical reagent grade or were chemically pure. The solvents were dried prior to use as needed. All the reactions were monitored by TLC.

4.1.1. Preparation of 4-amino-5-(trifluoromethyl)-4H-1,2,4-triazole-3-thiol (2)

A mixture of TCH (**1**) (10.6 g, 0.1 mol) and TFA (11.4 g, 0.1 mol) in water (30 mL) was refluxed for 5 h under stirring. The reaction solution was cooled and filtered. The filter residue was washed with cold water (10 mL) and recrystallized from water to give the pure compound **2**.

Colorless crystal; m.p. 140.3–141.0 °C; Yield: 85%; IR(KBr, cm^{-1}) ν: 3314, 3200, 1630, 1460, 1242, 1193, 1147, 1082, 1005, 764; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 11.64(s, 1H, SH), 4.83 (s, 2H, NH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −66.24 (s, 3F, $ArCF_3$); MS: *m*/*z* (%): 184[M^+](100), 126(11), 111(5), 96(8), 85(1), 78(12), 69(30), 60(23), 57(13), 45(8); Anal. Calcd. for $C_3H_3F_3N_4S$: C, 19.57; H, 1.64; N, 30.43. Found: C, 19.45; H, 1.59; N, 30.06.

4.1.2. General procedures for the synthesis of 4-amino-5-(4-substituted)phenyl)-4H-1,2,4-triazole-3-thiols (5a–b)

4-Fluorobenzoyl hydrazine (**3a**) (15.4 g, 0.1 mol) was added to a solution of potassium hydroxide (6.72 g, 0.12 mol) and absolute ethanol (200 mL) under stirring. After **3a** was dissolved, carbon disulfide (9.12 g, 0.12 mol) was added dropwise into the solution, the mixture was kept stirring at room temperature for 36 h. The precipitate was filtered and washed with dry ether (75 mL). The crude product potassium salt **4a** (13.4 g, 0.05 mol) was dissolved in hot water (50 mL) and filtered. Then, 85% hydrazine (5.8 g, 0.1 mol) and the filtrate containing the compound **4a** were refluxed for 4 h until the reaction mixture changed its color to green. A yellow solid was precipitated by diluting with cold water (150 mL) and acidifying with concentrated hydrochloric acid. After filtering, the solid was washed with cold water (20 mL), and recrystallized from ethanol to give the analytically pure compound **5a**. This method was suitable for the synthesis of compound **5b**.

4.1.2.1. 4-Amino-5-(4-fluorophenyl)-4H-1,2,4-triazole-3-thiol (5a). Yellow crystal; m.p. 205.7–205.8 °C; Yield: 35%; IR(KBr, cm^{-1}) ν: 3240, 3149, 1642, 1608, 1503, 1452, 1325, 1216, 1161, 1070, 1017, 953, 846, 731, 684; ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 13.95(s, 1H, SH), 8.09 (dd, *J* = 8.7, 5.6 Hz, 2H, PhH), 7.47–7.30 (m, 2H, PhH), 5.78 (s, 2H, NH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −108.21 to −108.28 (m, 1F, PhF); MS: *m*/*z* (%): 210[M^+](100), 139(30), 121(51), 109(16), 95(29) 75(11), 69(17), 57(28), 45(26); Anal. Calcd. for $C_8H_7FN_4S$: C, 45.71; H, 3.36; N, 26.65. Found: C, 45.53; H, 3.28; N, 26.51.

*4.1.2.2. 4-Amino-5-(4-(trifluoromethyl)phenyl)-4H-1,2,4-triazole-3-thiol (**5b**).* Yellow powder; m.p. 214.8–215.5 °C; Yield: 46%; IR(KBr, cm^{-1}) ν: 3280, 3144, 3011, 1618, 1540, 1508, 1471, 1323, 1153, 1118, 1064, 1017, 956, 847, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 10.86(s, 1H, SH), 8.32 (d, J = 8.2 Hz, 2H, PhH), 7.80 (d, J = 8.3 Hz, 2H, PhH), 4.90 (s, 2H, NH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −63.60 (s, 3F, $PhCF_3$); MS: m/z (%): 260[M^+](100), 241(5), 229(5), 189(22), 172(25), 145(23), 121(14), 113(3), 95(6), 81(5), 69(17), 60(25), 45(9); Anal. Calcd. for $C_9H_7F_3N_4S$: C, 41.54; H, 2.71; N, 21.53. Found: C, 41.67; H, 2.78; N, 21.47.

*4.1.3. General procedures for the synthesis of 3-(alkylthio)-5-substituted-4H-1,2,4-triazol-4-amines (**6a**–**i**)*

NaOH (0.6 g, 0.015 mol) and 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol (**2**, **5a**–**b**) (0.01 mol) were dissolved in water (15 mL). After the mixture was cooled to room temperature, the appropriate alkyl halide (0.012 mol) was added dropwise with stirring. The reaction mixture was stirred for 4 h (monitored by TLC), then the solid product was collected by filtration, washed with water and recrystallized from ethanol to give the title compounds **6a**–**i** with yields of 19–74% based on the corresponding compounds **2** and **5a**–**b**.

*4.1.3.1. 3-(Ethylthio)-5-(trifluoromethyl)-4H-1,2,4-triazol-4-amine (**6a**).* Colorless crystal; m.p. 75.4–76.4 °C; Yield: 33%; IR(KBr, cm^{-1}) ν: 3263, 3163, 2976, 2937, 1644, 1528, 1484, 1405, 1386, 1276, 1165, 1001, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 4.75 (s, 2H, NH_2), 3.36 (q, J = 7.4 Hz, 2H, CH_2CH_3), 1.50 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −64.24 (s, 3F, $ArCF_3$); MS: m/z (%): 212[M^+](38), 195(31), 184(100), 151(28), 138(23), 126(16), 111(11), 96(14), 69(45), 45(19); Anal. Calcd. for $C_5H_7F_3N_4S$: C, 28.30; H, 3.33; N, 26.40. Found: C, 28.59; H, 3.40; N, 26.51.

*4.1.3.2. 3-(Butylthio)-5-(trifluoromethyl)-4H-1,2,4-triazol-4-amine (**6b**).* Colorless crystal; m.p. 119.5–120.4 °C; Yield: 64%; IR(KBr, cm^{-1}) ν: 3285, 3178, 1956, 2938, 1626, 1526, 1489, 1404, 1274, 1185, 1161, 1001, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 4.74 (s, 2H, NH_2), 3.34 (t, J = 7.4 Hz, 2H, SCH_2CH_2), 1.85–1.77 (m, 2H, $SCH_2CH_2CH_2$), 1.55–1.46 (m, 2H, $CH_2CH_2CH_3$), 0.98(t, J = 7.4 Hz, 3H, CH_2CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −64.24 (s, 3F, $ArCF_3$); MS: m/z (%): 240[M^+](6), 207(9), 198(65), 184(100), 169(8), 149(41), 121(20), 111(15), 97(15), 85(33), 69(63), 57(83), 45(40); Anal. Calcd. for $C_7H_{11}F_3N_4S$: C, 35.00; H, 4.61; N, 23.32. Found: C, 34.87; H, 4.67; N, 23.45.

*4.1.3.3. 3-(Benzylthio)-5-(trifluoromethyl)-4H-1,2,4-triazol-4-amine (**6c**).* White powder; m.p. 143.0–144.3 °C; Yield: 66%; IR(KBr, cm^{-1}) ν: 3259, 3159, 3034, 2943, 1627, 1525, 1454, 1406, 1363, 1263, 1204, 1172, 1151, 1020, 780, 759, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.39–7.30 (m, 5H, PhH), 4.41 (s, 2H, NH_2), 4.38 (s, 2H, SCH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −64.48 (s, 3F, $ArCF_3$); MS: m/z (%): 274[M^+](11), 257(5), 149(3), 121(4), 106(8), 91(100), 77(3), 69(21), 57(3), 45(4); Anal. Calcd. for $C_{10}H_9F_3N_4S$: C, 43.79; H, 3.31; N, 20.43. Found: C, 43.92; H, 3.38; N, 20.56.

*4.1.3.4. 3-(Ethylthio)-5-(4-fluorophenyl)-4H-1,2,4-triazol-4-amine (**6d**).* Colorless crystal; m.p. 167.8–169.5 °C; Yield: 53%; IR(KBr, cm^{-1}) ν: 3244, 3140, 2986, 2928, 1608, 1528, 1484, 1462, 1380, 1240, 1157, 989, 841, 734, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.19 (dd, J = 8.8, 5.2 Hz, 2H, PhH), 7.17 (t, J = 8.6 Hz, 2H, PhH), 5.49 (s, 2H, NH_2), 3.26 (q, J = 7.4 Hz, 2H, SCH_2CH_3), 1.44 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −107.33 (s, 1F, PhF); MS: m/z (%): 238[M^+](48), 223(10), 210(100), 195(3), 179(4), 160(24), 139(33), 122(89), 109(12), 95(59), 75(30), 57(34), 45(11); Anal. Calcd. for $C_{10}H_{11}FN_4S$: C, 50.41; H, 4.65; N, 23.51. Found: C, 50.29; H, 4.63; N, 23.20.

*4.1.3.5. 3-(Butylthio)-5-(4-fluorophenyl)-4H-1,2,4-triazol-4-amine (**6e**).* White powder; m.p. 179.1 °C (decompose); Yield: 19%; IR(KBr, cm^{-1}) ν: 3260, 3136, 2964, 2932, 1647, 1605, 1535, 1481, 1450, 1382, 1233, 1160, 1096, 978, 835, 729, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.19 (dd, J = 8.7, 5.3 Hz, 2H, PhH), 7.17 (t, J = 8.6 Hz, 2H, PhH), 5.41 (s, 2H, NH_2), 3.24 (t, J = 7.4 Hz, 2H, SCH_2CH_2), 1.79–1.71 (m, 2H, $SCH_2CH_2CH_2$), 1.52–1.43 (m, 2H, $CH_2CH_2CH_3$), 0.96 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −110.59 to −110.66 (m, 1F, PhF); MS: m/z (%): 266[M^+](13), 251(11), 233(6), 219(98), 210(100), 206(20), 195(5), 179(7), 164(4), 149(6), 139(46), 122(70), 109(6), 95(37), 75(16), 57(16), 45(7); Anal. Calcd. for $C_{12}H_{15}FN_4S$: C, 54.12; H, 5.68; N, 21.04. Found: C, 53.97; H, 5.71; N, 21.29.

*4.1.3.6. 3-(Benzylthio)-5-(4-fluorophenyl)-4H-1,2,4-triazol-4-amine (**6f**).* Colorless powder; m.p. 175.6–176.4 °C; Yield: 74%; IR(KBr, cm^{-1}) ν: 3250, 3141, 2979, 1647, 1607, 1537, 1482, 1450, 1240, 1162, 1097, 987, 835, 716, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.04 (dd, J = 8.6, 5.4 Hz, 2H, PhH), 7.33–7.27 (m, 5H, PhH), 7.16 (t, J = 8.6 Hz, 2H, PhH), 4.33 (s, 2H, NH_2), 4.26 (s, 2H, SCH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −108.58 (s, 1F, PhF); MS: m/z (%): 300[M^+](22), 283(4), 267(1), 251(1), 178(5), 148(3), 121(25), 106(41), 91(100), 65(23), 57(5), 45(4); Anal. Calcd. for $C_{15}H_{13}FN_4S$: C, 59.98; H, 4.36; N, 18.65. Found: C, 59.62; H, 4.30; N, 18.39.

*4.1.3.7. 3-(Ethylthio)-5-(4-(trifluoromethyl)phenyl)-4H-1,2,4-triazol-4-amine (**6g**).* White powder; m.p. 178.7–179.1 °C; Yield: 60%; IR(KBr, cm^{-1}) ν: 3293, 3126, 2982, 2933, 1616, 1471, 1383, 1328, 1161, 1127, 1110, 1067, 1018, 975, 853, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.30 (d, J = 8.2 Hz, 2H, PhH), 7.73 (d, J = 8.3 Hz, 2H, PhH), 5.42 (s, 2H, NH_2), 3.30 (q, J = 7.4 Hz, 2H, SCH_2CH_3), 1.45 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −63.70 (s, 3F, $PhCF_3$); MS: m/z (%): 288[M^+](27), 274(9), 269(10), 260(100), 240(5), 229(5), 210(21), 189(16), 172(38), 145(43), 121(21), 95(9), 75(14), 57(21), 45(20); Anal. Calcd. for $C_{11}H_{11}F_3N_4S$: C, 45.82; H, 3.85; N, 19.44. Found: C, 45.97; H, 3.86; N, 19.21.

*4.1.3.8. 3-(Butylthio)-5-(4-(trifluoromethyl)phenyl)-4H-1,2,4-triazol-4-amine (**6h**).* White powder; m.p. 180.1–180.4 °C; Yield: 28%; IR(KBr, cm^{-1}) ν: 3264, 3147, 2965, 2935, 1621, 1442, 1391, 1328, 1170, 1127, 1067, 1017, 979, 846, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.32 (d, J = 8.2 Hz, 2H, PhH), 7.73 (d, J = 8.3 Hz, 2H, PhH), 5.49 (s, 2H, NH_2), 3.29 (t, J = 7.4 Hz, 2H, SCH_2CH_2), 1.79–1.71 (m, 2H, $SCH_2CH_2CH_2$), 1.51–1.39 (m, 2H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.3 Hz, 3H, CH_2CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −63.42 (s, 3F, $PhCF_3$); MS: m/z (%): 316[M^+](8), 297(6), 283(5), 269(93), 260(100), 256(19), 229(9), 214(2), 189(20), 172(31), 145(28), 121(19), 95(6), 75(6), 60(17), 57(14), 45(16); Anal. Calcd. for $C_{13}H_{15}F_3N_4S$: C, 49.35; H, 4.78; N, 17.72. Found: C, 49.65; H, 4.80; N, 17.86.

*4.1.3.9. 3-(Benzylthio)-5-(4-(trifluoromethyl)phenyl)-4H-1,2,4-triazol-4-amine (**6i**).* White powder; m.p. 202.9–203.8 °C; Yield: 53%; IR(KBr, cm^{-1}) ν: 3299, 3160, 3084, 3030, 2939, 1621, 1495, 1455, 1411, 1329, 1137, 1118, 1069, 1017, 977, 848, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.20 (d, J = 8.1 Hz, 2H, PhH), 7.73 (d, J = 8.2 Hz, 2H, PhH), 7.34–7.25 (m, 5H, PhH), 4.36 (s, 2H, NH_2), 4.26 (s, 2H, SCH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −63.47 (s, 3F, $PhCF_3$); MS: m/z (%): 350[M^+](18), 333(4), 317(1), 229(1), 171(4), 152(4), 145(7), 121(8), 106(29), 91(100), 77(5), 65(19), 45(4); Anal. Calcd. for $C_{16}H_{13}F_3N_4S$: C, 54.84; H, 3.74; N, 16.00. Found: C, 54.94; H, 3.69; N, 16.07.

4.1.4. Preparation of 3-(methylthio)-5-(trifluoromethyl)-4H-1,2,4-triazol-4-amine (6j)

Compound **2** (5.52 g, 0.03 mol), NaOH (2 g, 0.05 mol) and water (15 mL) were stirred at room temperature until solid was dissolved. Then CH_3I (5.68 g, 0.04 mol) was added dropwise into the solution with stirring. The reaction mixture was stirred for 0.5 h, and then filtered. The residue was recrystallized from ethanol to give **6j**.

Colorless crystal; m.p. 105.6–106.4 °C; Yield: 81%; IR(KBr, cm^{-1}) ν: 3352, 3283, 3200, 2938, 1638, 1529, 1403, 1383, 1267, 1204, 1145, 982, 878, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 4.76 (s, 2H, NH_2), 2.78 (s, 3H, CH_3S); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −64.21 (s, 3F, $ArCF_3$); MS: m/z (%): 198[M^+](25), 181(42), 149(30), 119(12), 97(24), 85(38), 69(100), 57(95), 45(31); Anal. Calcd. for $C_4H_5F_3N_4S$: C, 24.24; H, 2.54; N, 28.27. Found: C, 24.20; H, 2.49; N, 28.25.

4.1.5. Preparation of 3-(methylsulfonyl)-5-(trifluoromethyl)-4H-1,2,4-triazol-4-amine (7)

The compound **6j** (1.9 g, 0.01 mol) was added into glacial HOAc (8 mL), and then the solution was heated to 40 °C. After $NaWO_2{\cdot}H_2O$ (0.05 g) as a catalyst was added under stirring, the reaction mixture was heated to 50 °C. Next, 30% H_2O_2 (2.83 g, 0.025 mol) was added dropwise to the solution and the reaction temperature was kept at 50 °C until compound **6j** disappeared (observed by TLC). The mixture was poured into water (10 mL). The resulting precipitate was filtered and crystallized from water to afford the analytically pure compound **7**.

Colorless crystal; m.p. 147.7–148.6 °C; Yield: 37%; IR(KBr, cm^{-1}) ν: 3368, 3284, 3214, 2931, 1629, 1529, 1366, 1337, 1210, 1157, 956, 663, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 5.42 (s, 2H, NH_2), 3.61 (s, 3H, CH_3SO_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −63.80 (s, 3F, $ArCF_3$); MS: m/z (%): 230[M^+](10), 211(12), 181(4), 166(95), 150(48), 123(6), 111(14), 96(18), 81(16), 69(100), 57(42), 45(25); Anal. Calcd. for $C_4H_5F_3N_4O_2S$: C, 20.87; H, 2.19; N, 24.34. Found: C, 20.99; H, 2.23; N, 24.31.

4.1.6. Preparation of 3-(4-nitrophenoxy)-5-(trifluoromethyl)-4H-1,2,4-triazol-4-amine (8)

p-Nitrophenol (1.11 g 0.008 mol), NaOH (0.34 g, 0.0085 mol) and anhydrous toluene (20 mL) were refluxed for 3 h. Then the compound **7** (0.92 g, 0.004 mol) was added to the solution. The reaction mixture was refluxed for 8 h at which time the reaction was completed. After cooling, the mixture was filtered. The filtrate was washed twice with water (10 mL), twice with 20% sodium hydroxide solution (10 mL) and twice with water (10 mL). The organic layer was dried using anhydrous magnesium sulfate over night and filtered. The solvent was removed at reduced pressure to give compound **8** as a yellow powder, which was purified by recrystallization from ethanol.

Yellow powder; m.p. 150.9–151.0 °C; Yield: 28%; IR(KBr, cm^{-1}) ν: 3359, 3293, 3080, 1623, 1522, 1486, 1347, 1293, 1241, 1166, 1140, 999, 858; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.37 (d, J = 8.8 Hz, 2H, PhH), 7.74 (d, J = 9.0 Hz, 2H, PhH), 4.89 (s, 2H, NH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm): −64.91 (s, 3F, $ArCF_3$); MS: m/z (%): 289[M^+](13), 270(8), 259(7), 242(5), 207(3), 167(3), 149(8), 137(62), 122(20), 111(14), 92(19), 75(100), 63(29), 50(262), 45(9); Anal. Calcd. for $C_9H_6F_3N_5O_3$: C, 37.38; H, 2.09; N, 24.22. Found: C, 37.31; H, 2.07; N, 24.19.

4.2. Crystal structure determination

The single crystals of compounds **6g** and **7** were selected and glued on the tip of a glass fiber. Both cell dimensions and intensities were measured on a Bruker Smart APEX II CCD diffractometer with graphite monochromatized Mo Kα radiation (λ = 0.71073 Å) at 296(2) K. Both crystal structures were solved by direct methods SHELX-97 and refined using SHELXL-97 [25,26]. All the non-hydrogen atoms were refined by full-matrix least-squares technique on F^2 with anisotropic thermal parameters. All the hydrogen atoms were positioned geometrically and refined using a riding model, except the N–H hydrogen atoms of compound **6g** were located from the difference Fourier map and were set as isotropic. PLATON program was used for structure analysis and drawings preparation [27]. The selected crystallographic data are given in Table 3.

Table 3
Selected crystal data and refinement details of compounds **6g** and **7**.

Compd.	**6g**	**7**
Chemical formula	$C_{11}H_{11}F_3N_4S$	$C_4H_5F_3N_4O_2S$
FW	288.30	230.18
Crystal size (mm^3)	0.21 × 0.26 × 0.28	0.20 × 0.25 × 0.27
Color, shape	Colorless, block	Colorless, block
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
a (Å)	14.1323(16)	10.0642(13)
b (Å)	10.7066(12)	5.9384(8)
c (Å)	8.3446(10)	14.0629(18)
α (°)	90	90
β (°)	94.8630(10)	98.7970(10)
γ (°)	90	90
V ($Å^3$)	1258.1(3)	830.59(19)
Z	4	4
Density (calculated) (mg/m^3)	1.522	1.841
μ (mm^{-1})	0.286	0.423
F(000)	592	464
Reflections collected	9531	6756
Independent reflections	2474	1913
Observed [$I > 2\delta(I)$] reflections	2177	1813
No. of parameters	209	128
Goodness-of-fit	1.015	1.012
R_1 [$I > 2\delta(I)$]	0.0348	0.0433
ωR_2 [$I > 2\delta(I)$]	0.0986	0.1234
Largest diff. peak and hole ($e Å^{-3}$)	0.238 and −0.232	0.681 and −0.653

The crystallographic data have been deposited with Cambridge Crystallographic Data Centre, CCDC No. 844716 for the compound **6g** and CCDC No. 844715 for the compound **7**. Copies of this information can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).

4.3. Fungicidal assay

The inhibition effects of the title compounds **2**, **5a–b**, **6a–j**, **7** and **8** against phytopathogenic fungi (*R. solani*, *F. graminearum*, *B. cinerea* and *C. capsici*) were tested using a radial growth inhibition technique according to the reported method [28]. Each compound was diluted with MeOH (0.5 mL) and added to potato sucrose agar medium (PSA) respectively to obtain a concentration of 100 μg/mL before pouring into the Petri dishes. Each compound was tested in triplicate. The parallel controls were maintained with MeOH (0.5 mL) mixed with PSA medium. The discs of mycelia felt (0.5 cm diameter) of fungi were transferred aseptically to the center of Petri dishes. The treatments were incubated at 25 ± 1 °C in the dark. The diameters of the colonies were measured after the colonies in the control treatments had covered two-thirds of the Petri dishes. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I was the growth inhibition rate (percent), C was the colony diameter of the parallel control (mm), and T was the colony diameter of the title compound treatment (mm).

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