Research Article

Synthesis, Crystal Structure, and Fungicidal Activity of 5-(4-cyclopropyl-5-((3-fluorobenzyl)thio)-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole

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A new 1,2,3-thiadiazole compound was synthesized and characterized. The crystal structure of the title compound ($C_{15}H_{14}FN_5S_2$, $M_r = 347.43$) has been determined by single-crystal X-ray diffraction. The crystal is of triclinic, space group P-1 with $a = 7.0490(14)$, $b = 9.0212(18)$, $c = 12.799(3)$ Å, $\alpha = 89.97(3)^\circ$, $\beta = 82.27(3)^\circ$, $\gamma = 73.17(3)^\circ$, $V = 771.3(3)$ Å³, $Z = 2$, $F(000) = 360$, $D_c = 1.496$ g/cm³, $\mu = 0.036$ mm⁻¹, the final $R_1 = 0.0358$, and $wR_2 = 0.0986$ for 2204 observed reflections with $I > 2\sigma(I)$. A total of 5697 reflections were collected, of which 2719 were independent ($R_{int} = 0.0028$). The herbicidal activity of title compound was determined; the results showed that the title compound displayed excellent fungicidal activity.

1. Introduction

In recent years, heterocyclic compounds have received considerable attention because of their pharmacological and pesticidal importance [1–5]. 1,2,3-Thiadiazole moiety has been claimed to have beneficial medicinal and agricultural applications, because they exhibited excellent biological activities such as fungicidal activities [6], anti-HBV [7], herbicidal activity [8], antiamebic activity [9], and KARI activity [10]. The 1,2,3-thiadiazole has been widely studied as they are useful intermediates in organic synthesis. For example, after the plant inducers such as thiadinal [11], BTH [12], was discovered (Figure 1), 1,2,3-thiadiazoles pesticide has become one of the focus of developing agrochemicals in academia and industries. Furthermore, 1,2,4-triazoles exhibited a diverse range of bioactivities in medicinal and agrochemical field, such as fungicidal [13], anti-HCV [14], anticancer [15], antifungal [16], and antimicrobial [17] agents. Some compounds have been developed as commercial fungicides (Figure 2), such as Triadimefon, Triadimenol, Flusilazole, and so on. Due to their diverse properties, 1,2,4-triazole fungicides may become one of the focuses in drug research. Also, the cyclopropane is an active group which exists in many compounds [18–21].

In view of the facts mentioned above, and also as a part of our work [22] on the synthesis of bioactive compounds, the title compounds were designed by introducing cyclopropane and 1,2,3-thiadiazole pharmacophore into 1,2,4-triazole scaffold. Some 1,2,4-triazole derivatives were synthesized and characterized by ¹H NMR, MS, and elemental analysis. The single crystal structure of the title compound was determined by X-ray diffraction. The fungicidal activities of these compounds were tested.

2. Materials and Methods

2.1. Instruments. Melting points were determined using an X-4 apparatus and are uncorrected. ¹H NMR spectra were measured on a Bruker AV-400 instrument using TMS as an internal standard and CDCl₃ as the solvent. Elemental analyses were performed on a Vario EL elemental analyzer. Crystallographic data of the compound were collected on a Rigaku Saturn diffractometer. All the reagents are of analytical grade or freshly prepared before use.

2.2. Synthesis. The title compounds were synthesized according to the route shown in Scheme 1, and the yields were not optimized.

FIGURE 1: Molecular structure of the title compound, showing displacement ellipsoids drawn at the 30% probability level.

FIGURE 2: The packing of title compound.

Intermediate 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (**5**) was synthesized according to the literature [6]. A mixture of acylhydrazine (**5**) with isothiocyanatocyclopropane (**6**) (1.5 g) was refluxed for 3 h in ethanol. After cooling down to room temperature, the products were obtained and recrystallized from methanol to give **7**. A mixture of a compound (**7**) (10 mmol) in aqueous NaOH solution (5 mL, 2 N) was refluxed for 4 h. After cooling down to room temperature, HCl aqueous solution (4 N) was added to afford a large amount of precipitate. The solid was filtered, dried, and recrystallized from methanol to give intermediate (**8**). To a stirred solution of (**8**) (5.1 mmol) and K_2CO_3 (0.2 g, 5.6 mmol) in DMF (15 mL), a mixture of a 2-fluorobenzyl chloride (5.6 mmol) was added dropwise. The resulting mixture was stirred at room temperature for overnight. The mixture was poured into water. The precipitate formed was filtered off and recrystallized from petroleum ether/acetone to give (**9**) in good yields. white crystal, yield, 86%; mp, 124–125°C; Anal. Calcd for $C_{15}H_{14}FN_5S_2$ (%): C, 51.85; H, 4.06; N, 20.16. Found: C, 51.78; H, 4.21; N, 20.13;

^1H NMR (400 MHz, $CDCl_3$), 0.84–0.88 (m, 2H, cyclopropane- CH_2), 1.17–1.23 (m, 2H, cyclopropane- CH_2), 3.01 (s, 3H, Het- CH_3), 3.02–3.06 (m, 1H, cyclopropane-CH), 4.57 (s, 2H, CH_2), 6.96–7.01 (m, 1H, Ph-H), 7.18–7.36 (m, 3H, Ph-H); ESI-MS: 694.55 $[2M]^+$, 348.10 $[M+H]^+$.

2.3. Structure Determination. The cube-shaped single crystal of the title compound was obtained by recrystallization from EtOH. The crystal with dimensions of 0.18 mm $\times$ 0.12 mm $\times$ 0.10 mm was mounted on a Rigaku Saturn diffractometer with a graphite-monochromated MoK α radiation ($\lambda = 0.71073$ Å) by using a Φ scan modes at 113(2) K in the range of $1.61^\circ \leq \theta \leq 25.01^\circ$. A total of 5697 reflections were collected, of which 2719 were independent ($R_{int} = 0.0278$) and 2204 were observed with $I > 2\sigma(I)$. The calculations were performed with SHELXS-97 program [23] and the empirical absorption corrections were applied to all intensity data. The nonhydrogen atoms were refined anisotropically. The hydrogen atoms were determined with theoretical calculations and refined isotropically. The final full-matrix least squares refinement gave $R = 0.0358$ and $wR = 0.0986$ ($w = 1/[\sigma^2(F_o^2) + (0.0635P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$), $S = 1.07$, $(\Delta/\sigma)_{max} = 0.0001$, $\Delta\rho_{max} = 0.24$, and $\Delta\rho_{min} = -0.29$ e Å $^{-1}$. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-Ray Crystallography [24]. A summary of the key crystallographic information is given in Table 1.

3. Results and Discussion

3.1. Synthesis and Spectra. The synthetic procedures for title compounds are shown in Scheme 1. All the synthesized intermediates reacted with the next materials without purification. The thioether intermediates **9** were synthesized by stirring triazole sulfide intermediate **8** with 3-fluoro benzyl chloride at room temperature for 24 hours. The proton magnetic resonance spectra of the 1,2,3-thiadiazole have been recorded in $CDCl_3$. The thioamide ($-NH-C(=S)$) structure of triazole intermediates can exist either as the thione, or thiol tautomeric form. In ^1H NMR spectrum the singlet at

SCHEME 1: The synthetic route of title compound.

δ 10.86 ppm corresponds to the SH proton indicating that in solution **8** exists in the thiol tautomeric form versus the thione form [25]. The signals at 3.0 ppm range are methyl signals of 1,2,3-thiadiazole. With regard to the mass spectra, the title compounds showed M-H signals. The measured data of elemental analytical results is in accord with the theoretical values.

3.2. Crystal Structure. The selected bond lengths and bond angles are shown in Table 2. The molecular structure of the title compound is shown in Figure 1. The molecular packing of the molecule is shown in Figure 2.

Generally, the average bond lengths and bond angles of ring system (phenyl, cyclopropane, triazole, and 1,2,3-thiadiazole) are normal. However, the C2=N2 bond [1.371(3) Å] and C4=N3 [1.314(3) Å] are longer than the general C=N double bond length of 1.28 Å [26, 27]. The C–C bond length of 1,2,3-thiadiazole group is 1.385(3) Å. In the other plane cyclopropane ring and phenyl ring, the C–C bond lengths range from 1.374(3) to 1.502(3) Å, almost equal to the values of typical bonds of aromatic structure [28–30] and alkyl structure. The bond angles of phenyl ring vary from 117.95(19) to 123.09(18)° with the average of 120° and the bond angles of the other cyclopropane ring change from 59.71(14) to 60.38(14)°, also with the average of 60°. Also, the bond angles of 1,2,4-triazole ring and 1,2,3-thiadiazole ring are from 104.16(16) to 107.69(15)° and 93.64(10) to 114.00(18)°, respectively. The torsion angle of thioether group C5–S2–C9–C10 is 177.05(13)°.

As shown in Figure 1, the 1,2,3-thiadiazole ring is nearly planar with 1,2,4-triazole ring with a quite small dihedral angle (θ) of 13.3°. The triazole ring (N3, N4, C5, N5, C4) and thiadiazole ring (N1, N2, S1, C3, C2) are fairly planar with plane equation $-0.962x + 6.339y + -7.876z = 1.1720$ and $0.669x + 7.212y + -7.645z = 2.1323$, respectively, and the largest deviation from the least squares plane is 0.0057 nm

TABLE 1: Crystal structure and data refinement parameters.

Empirical formula	C ₁₅ H ₁₄ FN ₅ S ₂
Formula weight	347.43
Crystal system/space group	Triclinic, P-1
<i>a</i> (Å)	7.0490(14)
<i>b</i> (Å)	9.0212(18)
<i>c</i> (Å)	12.799(3)
α (°)	89.97(3)
β (°)	82.27(3)
γ (°)	73.17(3)
<i>V</i> (Å ³)	771.3(3)
<i>Z</i>	2
<i>D</i> _{calc} (g/cm ³)	1.496
μ (mm ⁻¹)	0.3600
Crystal size (mm)	0.18 × 0.12 × 0.10
Color/shape	Colorless/cube
Temp (K)	113 (2)
Theta range for collection	1.6–27.8°
Reflections collected	5697
Independent reflections	2719
Data/restraints/parameters	2719/12/219
Goodness of fit on <i>F</i> ²	1.066
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0358, <i>wR</i> ₂ = 0.0986
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0446, <i>wR</i> ₂ = 0.1040
Largest difference peak/hole	0.242 and –0.295

and 0.0028 nm. Meanwhile, the phenyl ring is vertically with both the 1,2,3-thiadiazole ring, and the 1,2,4-triazole ring with the respective dihedral angles of 71.8° and 84.9°. Also, it is observed that the cyclopropane ring is vertical with 1,2,3-thiadiazole ring, 1,2,4-triazole ring and phenyl ring with the dihedral angle of 108.0°, 121.3°, and 38.8°.

TABLE 2: Selected bond lengths (Å) and bond angles (°).

Bond	Dist.	Angle	(°)
S(1)–N(1)	1.6679(19)	N(1)–S(1)–C(3)	93.64(10)
S(1)–C(3)	1.697(2)	C(5)–S(2)–C(9)	100.28(10)
S(2)–C(5)	1.743(2)	N(2)–N(1)–S(1)	111.43(15)
S(2)–C(9)	1.814(2)	N(1)–N(2)–C(2)	114.00(18)
F(1)–C(12)	1.336(2)	C(4)–N(3)–N(4)	107.69(15)
F(1')–C(14)	1.193(6)	C(5)–N(5)–C(4)	104.16(16)
N(1)–N(2)	1.307(2)	C(5)–N(5)–C(6)	127.06(17)
N(2)–C(2)	1.371(3)	N(2)–C(2)–C(1)	119.06(18)
N(3)–C(4)	1.314(3)	C(3)–C(2)–C(1)	127.53(19)
N(3)–N(4)	1.397(2)	C(2)–C(3)–C(4)	126.78(19)
N(4)–C(5)	1.314(3)	C(2)–C(3)–S(1)	107.53(16)
N(5)–C(5)	1.367(3)	C(4)–C(3)–S(1)	125.60(15)
N(5)–C(4)	1.382(2)	N(3)–C(4)–N(5)	110.21(17)
N(5)–C(6)	1.455(2)	N(3)–C(4)–C(3)	124.80(18)
C(1)–C(2)	1.488(3)	N(4)–C(5)–N(5)	111.48(17)
C(2)–C(3)	1.385(3)	N(4)–C(5)–S(2)	127.65(16)
C(3)–C(4)	1.451(3)	C(7)–C(8)–C(6)	59.90(14)
C(6)–C(7)	1.494(3)	C(10)–C(9)–S(2)	106.41(13)

3.3. Fungicidal Activity. Fungicidal activity of title compound against *Cladosporium cucumerinum*, *Corynespora cassiicola*, *Sclerotinia sclerotiorum*, *Erysiphe cichoracearum*, and *Colletotrichum orbiculare* was evaluated according to [31], and a potted plant test method was adopted. The primary bioassay results showed that the title compounds exhibited good inhibition abilities against *Corynespora cassiicola* (86%) and *Colletotrichum orbiculare* (82%) at 500 µg/mL respectively. It displayed the lower activity against *Cladosporium cucumerinum* (13%) and *Sclerotinia sclerotiorum* (5%). It also exhibited moderate inhibition against *Erysiphe cichoracearum* (48%).

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