LETTER

Synthesis, Crystal Structure and Fungicidal Activity of 3,4-Dichloro-5-(6-chloro-9-(4-fluorobenzyl)-9*H*-purin-8-yl)isothiazole①

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ABSTRACT 3,4-Dichloro-5-(6-chloro-9-(4-fluorobenzyl)-9*H*-purin-8-yl)isothiazole, a novel purine derivative, was synthesized by the cyclization of pyrimidine amine. Its structure was characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, H RMS and single-crystal X-ray diffraction. This compound **3** is crystallized from a mixed solvent of dichloromethane and *n*-hexane (1:2, v/v) for structural identification as monoclinic crystal system, space group $P2_1/n$ with a = 11.66250(10), b = 8.21300(10), c = 17.77920(10) Å, V = 1676.34(3) Å^3, Z = 4, D_c = 1.643 g/cm^3, F(000) = 832.0 and μ = 6.301 mm^{-1}. 22315 reflections were measured (8.43≤2θ≤158.10°), of which 3532 were unique (R_{int} = 0.0311) and used in all calculations. The final R = 0.0334 ($I > 2\sigma(I)$) and wR = 0.0842 (reflections). The title compound showed over 50% of growth inhibition against *Botrytis cinereal*, *Cercospora arachidicola*, *Gibberella zeae*, *Rhizoctonia solani* and *Sclerotinia sclerotiorum* at 50 mg/L, and its EC_{50} value against *R. solani* was 60.44 μmol/L, which was active at the same level as that of positive control diflumetorim with its EC_{50} value of 60.29 μmol/L and less active than **YZK-C22** with its EC_{50} value of 12.32 μmol/L, respectively. Our studies discovered that the combination of bioactive substructures of isothiazole with purine could be an effective way to novel fungicide development.

Keywords: purine, synthesis, crystal structure, fungicidal activity;
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1 INTRODUCTION

The purine (imidazo-[4,5-d]pyrimidine) skeleton is an important structural motif which plays an important role in different life related processes[1, 2]. During the wide range of biological activities, purine structure is considered as a privileged scaffold in medicinal chemistry. Many drugs containing purine fragment have been developed for the treatment of asthma, inflammation, cancer and gastrointe stinal diseases[3-9]. In addition, some compounds with purine fragment, such as aureonuclemycin, are fungicides for plant disease control[10]. As active substructures, heterocyclic ring structures with both S and N atoms[11], especially 3,4-dichlo roisothiazole[12], showed good systemic acquired resistance and fungicidal activities in pesticide lead discovery.

The discovery of lead compounds is an important basis for

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novel pesticide development. Our group focused on agrichemical lead discovery, different pyrazole-thiazoles[13], pyrazole-aromatics[14], and thiadiazole derivatives[15] were found to show various degrees of fungicidal activity. **YZK-C22** is a highly active fungicidal lead[16]. The research has shown that **YZK-C22** does not act at traditional pesticide targets, but has a new potent target: pyruvate kinase (PK)[17]. Based on the structure of the lead molecule **YZK-C22** and its potent new target PK, 3,4-dichloro-5-(6-chloro-9-(4-fluoro benzyl)-9*H*-purin-8-yl)isothiazole was rationally designed (Fig. 1) and synthesized (Scheme 1) by the combination of bioactive substructures of purine and isothiazole, and its crystal chemical structure and fungicidal activity were evaluated here.

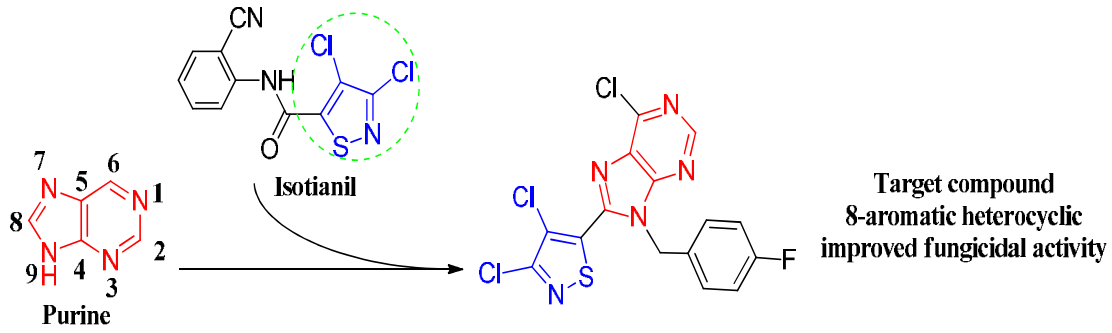


Fig. 1. Design of the target compound

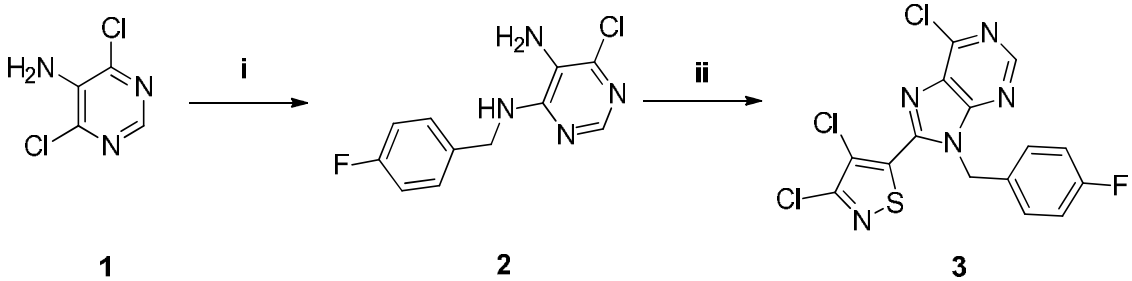
2 EXPERIMENTAL

2. 1 Instruments and reagents

Melting point was measured on an X-4 Digital Type Melting Point Tester (Gongyi, China) and uncorrected. ^{1}H NMR spectra were recorded on a Bruker AV400 spectro meter (400 MHz) (Wisconsin, United States of America) and chemical shifts were reported in ppm. ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer (101 MHz) (Wisconsin, United States of America) with complete proton decoupling. ^{19}F NMR spectra were recorded on a Bruker AV400 spectrometer (101 MHz) (Wisconsin, United States of America) with complete proton decoupling. High-resolution mass spectra (HRMS) were recorded with an Agilent 6520 Q-TOF LC/MS instrument (Agilent Technologies Inc. State of California, United States of America). Crystal structure was determined on a Rigaku Xtalab P200 diffractometer. All of the solvents and materials were of reagent grade and purified as required.

2. 2 Synthetic procedure for the target compound

The procedure for the synthesis of compound **3** is shown in Scheme 1. As a key intermediate, pyrimidine amine **2** was synthesized according to the revision of the reported method[5]. Triethylamine (1.00 mL, 7.37 mmol) was added to a suspension of compound **1** (98% content) (1.00 g, 6.14 mmol) in ethanol (10 mL), followed by the addition of 4-fluorobenzylamine (0.75 mL, 6.45 mmol). Then the reaction mixture was stirred for 18 h at 80 °C. After the reactant was consumed, the reaction mixture was concentrated under reduced pressure to remove the solvent, and the intermediate **2** was obtained by purifying the crude residue using silica gel column chromatography with a mixture eluent of petroleum ether (60~90 °C fraction):ethyl acetate (2:1, *v*/*v*).



Reagents and conditions: (i) 4-fluorobenzylamine, EtOH, Et_3N, 80 °C, 12 h (ii) 3,4-dichloroisothiazole-5-carbonyl chloride, NH_4Cl, toluene, 100 °C, 2 h; $POCl_3$, 100 °C, 12 h

Scheme 1. Synthesis of the target compound 3

Analytical data for intermediate **2**. Yellow solid; yield, 25%; m.p.: 221~223 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (s, 1H), 7.39~7.30 (m, 3H), 7.19~7.09 (m, 2H), 5.09 (s, 2H), 4.60 (d, J = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.2 (d, $^1J_{F\text{-}C}$ = 242.2 Hz), 151.7, 145.5, 136.9, 135.6 (d, $^4J_{F\text{-}C}$ = 3.0 Hz), 129.3 (d, $^3J_{F\text{-}C}$ = 8.2 Hz), 123.6, 115.0 (d, $^2J_{F\text{-}C}$ = 21.2 Hz), 43.4. ^{19}F NMR (101 MHz, $CDCl_3$) δ –114.59. HRMS (ESI) m/z calcd. for $C_{11}H_{11}ClFN_4^+$ $(M+H)^+$: 253.0651; found: 253.0649. Document[18] reported its yield of 84% with the m.p. of 240~242 °C.

Compound **3** was synthesized according to the revision of the reported method[19]. To a suspension of compound **2** (0.20 g, 0.79 mmol) in toluene, ammonium chloride (0.25 g, 4.74 mmol) and 3,4-dichloroisothiazole-5-carbonyl chloride (0.10 mL, 0.79 mmol) were added successively. The reaction mixture was heated at 100 °C for 2 h. After cooling the mixture to room temperature, phosphorus oxychloride (8.0 mL) was added. Then, the mixture was slowly heated to 100 °C again and kept for 12 h. After the reaction completed, the reaction mixture was slowly dropwise added to ice water. Then, the pH of the mixture was adjusted to 7~8 using ammonia water (25%~28%) carefully, and compound **3** in the mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with saturated sodium chloride solution (20 mL) for 3 times and dried over anhydrous sodium sulfate. After the solvent evaporation under reduced pressure, the residue of the target compound **3** was purified by silica gel column chromatography with a mixture of petroleum ether:ethyl acetate (5:1, *v*/*v*) as eluent.

Analytical data for compound **3**. Yellow solid; yield, 81%; m.p.: 133~134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 6.99~6.92 (m, 2H), 6.92~6.85 (m, 2H), 5.53 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{F\text{-}C}$ = 248.9 Hz), 153.1, 152.9, 152.0, 149.4, 148.8, 143.7, 131.5, 130.0 (d, $^4J_{F\text{-}C}$ = 3.2 Hz), 129.3 (d, $^3J_{F\text{-}C}$ = 8.2 Hz), 124.2, 116.2 (d, $^2J_{F\text{-}C}$ = 21.8 Hz), 47.2. ^{19}F NMR (101 MHz, $CDCl_3$) δ –111.9. HRMS (ESI) m/z calcd. for $C_{15}H_8Cl_3FN_5S^+$ $(M+H)^+$: 413.9545; found: 413.9549.

2. 3 Structure determination

The colorless crystal of the title compound **3** with dimensions of 0.18mm × 0.16mm × 0.13mm was cultured from *n*-hexane/dichloromethane and selected for X-ray diffraction analysis. The data were collected on a Rigaku Xtalab P200 Single Crystal diffractometer equipped with mirror-monochromatic Cu$K\alpha$ radiation (λ = 1.54184 Å) with an ω scan mode at 294.15 K. In the range of $4.22 \leqslant \theta \leqslant 79.05°$, a total of 22315 reflections were collected with 3532 unique ones (R_{int} = 0.0311), of which 3238 were observed with $I > 2\sigma(I)$ for refinements. Using Olex2[20], the structure was solved by the ShelXT[21] structure solution program using Intrinsic Phasing and refined with the ShelXL[22] refinement package using Least Squares minimization. All of the non-hydrogen atoms were located with successive difference Fourier syntheses. The hydrogen atoms were added according to theoretical models. The final full-matrix least-squares refinement converged at R = 0.0310, wR = 0.0842 ($w = 1/[\sigma^2(F_o)^2 + (0.0393P)^2 + 0.5096P]$, where $P = (F_o^2 + 2F_c^2)/3$), S = 1.075, $(\Delta\rho)_{max}$ = 0.24, $(\Delta\rho)_{min}$ = –0.25 e/Å^3 and $(\Delta/\sigma)_{max}$ = 0.001.

2. 4 Fungicidal activity determination

The fungicidal activities of intermediate **2** and target compound **3** were evaluated at 50 mg/L according to the previously reported procedures[23-25]. Seven representative fungi, *A. s*: *Alternaria solani*; *B. c*: *Botrytis cinerea*; *C. a*: *Cercospora arachidicola*; *G. z*: *Gibberella zeae*; *P. p*: *Physalospora piricola*; *R. s*: *Rhizoctonia solani* and *S. s*: *Sclerotinia sclerotiorum*, were tested. The commercially available pyrimidinamine fungicide diflumetorim and lead molecule **YZK-C22** were selected as positive controls. Inhibitory rates (%) = $(D_{control} - D_{test})/(D_{control} - 4) \times 100$, where $D_{control}$ was the average diameter (mm) of mycelia in the absence of any compounds and D_{test} was the average diameter (mm) of mycelia treated with the test compound. All experiments were tested in triplicates. Data were presented as the mean ± standard deviation. EC_{50} of the target compound **3** and corresponding positive controls against *R. solani* were evaluated, too[16].

3 RESULTS AND DISCUSSION

As shown in Scheme 1, the target compound **3** was synthesized in good yield by cyclization of pyrimidine amine **2** with 3,4-dichloroisothiazole-5-carbonyl chloride. Its structure was characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. The crystal structure of compound **3**, crystallizing from a mixed solvent of dichloromethane and *n*-hexane (1:2, v/v), is shown in Fig. 2.

The selected bond lengths, bond angels and torsional angels of compound **3** are shown in Tables 1 and 2. The bond lengths and angles of the isothiazole ring agreed well with the values reported[26]. Meanwhile, bond lengths and angles of the purine substructure appeared to be normal relative to the

closely related compounds in literature[27]. The sum of C(4)–N(5)–C(9), C(8)–N(5)–H(9) and C(8)–N(5)–H(5) angles was 359.96°, indicating the sp^2 hybridization state of N(5) atom. The torsion angle of N(2)–C(5)–C(8)–N(4) is –178.75°, indicating that the whole purine was coplanar. The torsion angles of C(2)–C(3)–C(4)–N(2) and C(8)–N(5)–C(9)–C(10) are –67.7° and 121.03°, which means that both the isothiazole and benzene rings were nonplanar with the purine ring. As shown in Table 3, the intermolecular hydrogen bonds C(9)–HA(9)···F(1)^{i}, C(9)–HA(9)···Cl(2)^{ii} and C(9)–HB(9)···N(2)^{iii} were found in compound **3**, which lead to the position of benzene ring close to the isothiazole ring rather than the purine ring. These intermolecular hydrogen bonds stabilize the crystal packing (Fig. 3). In addition, the intermolecular C–H···π interaction of C(12)–H(12)···C(15)^{iv} (H(12)···C(15)^{iv} 2.676 Å) was also observed in the crystal packing of compound **3**, which is two-dimensional. No π-π interaction was observed due to the large distance between adjacent benzene ring and isothiazole ring or purine ring.

Table 1. Selected Bond Lengths (Å) and Bond Angles (°) for Compound 3

Bond	Dist.	Bond	Dist.	Bond	Dist.
Cl(1)–C(1)	1.7125(17)	N(3)–C(7)	1.347(3)	C(5)–C(6)	1.391(2)
Cl(2)–C(2)	1.7046(17)	N(4)–C(7)	1.334(2)	C(5)–C(8)	1.392(2)
Cl(3)–C(6)	1.7244(19)	N(4)–C(8)	1.333(2)	C(9)–C(10)	1.509(2)
S(1)–N(1)	1.6466(15)	N(5)–C(4)	1.3753(19)	C(10)–C(11)	1.382(2)
S(1)–C(3)	1.7064(16)	N(5)–C(8)	1.3720(19)	C(10)–C(15)	1.385(2)
F(1)–C(13)	1.3618(19)	N(5)–C(9)	1.4697(19)	C(11)–C(12)	1.381(2)
N(1)–C(1)	1.301(2)	C(1)–C(2)	1.414(2)	C(12)–C(13)	1.362(3)
N(2)–C(4)	1.3164(19)	C(2)–C(3)	1.362(2)	C(13)–C(14)	1.360(3)
N(2)–C(5)	1.378(2)	C(3)–C(4)	1.466(2)	C(14)–C(15)	1.390(3)
N(3)–C(6)	1.314(2)				
Angles	(°)	Angles	(°)	Angles	(°)
N(1)–S(1)–C(3)	95.25(8)	C(2)–C(3)–S(1)	108.45(11)	N(4)–C(8)–C(5)	126.88(15)
C(1)–N(1)–S(1)	109.11(12)	C(2)–C(3)–C(4)	124.94(15)	N(5)–C(8)–C(5)	105.65(13)
C(4)–N(2)–C(5)	103.45(13)	C(4)–C(3)–S(1)	126.29(12)	N(5)–C(9)–C(10)	112.86(12)
C(6)–N(3)–C(7)	117.55(15)	N(2)–C(4)–N(5)	114.21(13)	C(11)–C(10)–C(9)	120.87(14)
C(8)–N(4)–C(7)	111.53(16)	N(2)–C(4)–C(3)	124.18(14)	C(11)–C(10)–C(15)	118.91(14)
C(4)–N(5)–C(9)	128.24(13)	N(5)–C(4)–C(3)	121.24(13)	C(15)–C(10)–C(9)	120.21(14)
C(8)–N(5)–C(4)	105.51(12)	N(2)–C(4)–C(6)	134.17(16)	C(12)–C(11)–C(10)	120.81(15)
C(8)–N(5)–C(9)	126.21(13)	N(2)–C(4)–C(8)	111.16(13)	C(13)–C(12)–C(11)	118.53(17)
N(1)–C(1)–Cl(1)	120.31(13)	C(6)–C(5)–C(8)	114.63(15)	F(1)–C(13)–C(12)	118.51(18)
N(1)–C(1)–C(2)	116.91(15)	N(3)–C(6)–Cl(3)	118.19(13)	C(14)–C(13)–F(1)	118.62(17)
C(2)–C(1)–Cl(1)	122.77(14)	N(3)–C(6)–C(5)	121.36(17)	C(14)–C(13)–C(12)	122.87(16)
C(1)–C(2)–Cl(2)	124.57(13)	C(5)–C(6)–Cl(3)	120.45(15)	C(13)–C(14)–C(15)	118.27(16)
C(3)–C(2)–Cl(2)	125.10(13)	N(4)–C(7)–N(3)	128.05(17)	C(10)–C(15)–C(14)	120.61(16)
C(3)–C(2)–C(1)	110.26(15)	N(4)–C(8)–N(5)	127.46(15)		

Table 2. Selected Torsional Angles (°) for Compound 3

Angle	(°)	Angle	(°)
Cl(1)–C(1)–C(2)–Cl(2)	–0.2(2)	C(4)–N(5)–C(9)–C(10)	–56.3(2)
Cl(2)–C(2)–C(3)–C(4)	4.5(2)	C(5)–N(2)–C(4)–C(3)	172.27(15)
S(1)–N(1)–C(1)–Cl(1)	–177.56(10)	C(6)–C(5)–C(8)–N(4)	–0.7(2)
S(1)–C(3)–C(4)–N(5)	–67.76(19)	C(6)–C(5)–C(8)–N(5)	178.55(14)
F(1)–C(13)–C(14)–C(15)	–179.32(18)	C(7)–N(3)–C(6)–Cl(3)	179.48(15)
N(1)–S(1)–C(3)–C(4)	172.91(14)	C(8)–N(5)–C(4)–C(3)	–172.18(14)
N(1)–C(1)–C(2)–Cl(2)	–178.53(13)	C(8)–N(5)–C(9)–C(10)	121.03(16)
N(2)–C(5)–C(6)–Cl(3)	–1.5(3)	C(9)–N(5)–C(4)–N(2)	178.92(14)
N(2)–C(5)–C(8)–N(4)	–178.75(15)	C(9)–N(5)–C(4)–C(3)	5.6(2)
N(2)–C(5)–C(8)–N(5)	0.48(18)	C(9)–N(5)–C(8)–N(4)	0.5(3)

To be continued

N(5)–C(9)–C(10)–C(11)	–49.3(2)	C(9)–C(10)–C(11)–C(12)	–178.15(16)
N(5)–C(9)–C(10)–C(15)	131.96(16)	C(9)–C(10)–C(15)–C(14)	177.84(17)
C(2)–C(3)–C(4)–N(2)	–67.7(2)	C(11)–C(12)–C(13)–F(1)	179.01(18)
C(2)–C(3)–C(4)–N(5)	104.98(18)	C(13)–C(14)–C(15)–C(10)	0.6(3)
C(4)–N(5)–C(8)–N(4)	178.30(15)	C(15)–C(10)–C(11)–C(12)	0.6(3)

Table 3. Hydrogen Bond Lengths (Å) and Bond Angles (°) for Compound 3

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠(DHA)
C(9)–H(9A)···F(1)^{i}	0.97	2.59	3.422(2)	144
C(9)–H(9A)···Cl(2)^{ii}	0.97	2.94	3.555(2)	123
C(9)–H(9B)···N(2)^{iii}	0.97	2.68	3.612(2)	162

Symmetry codes: i: –1/2 + *x*, 1/2 – *y*, –1/2 + *z*; ^{ii}: –*x*, 1 – *y*, – *z*; ^{iii}: –1.5 + *x*, 1/2 – *y*, –1/2 + *z*

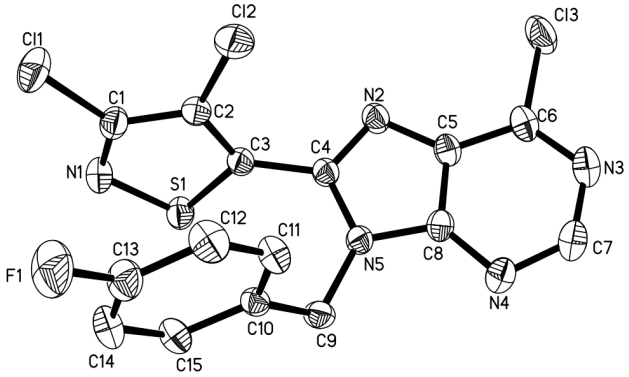


Fig. 2. X-ray crystal structure of compound 3

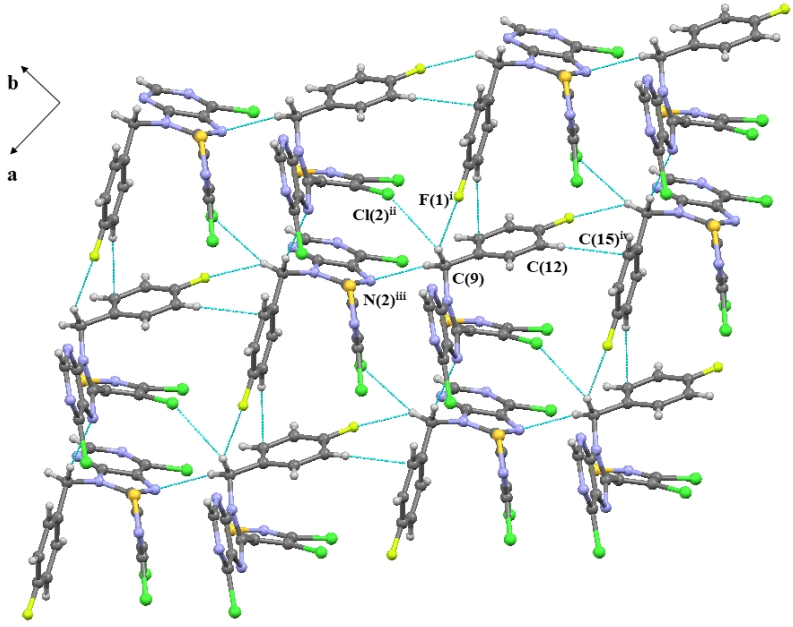


Fig. 3. Crystal packing of compound 3

Symmetry codes: ^{i}: –1/2 + *x*, 1/2 – *y*, –1/2 + *z*; ^{ii}: –*x*, 1 – *y*, –*z*; ^{iii}: –3/2 + *x*, 1/2 – *y*, –1/2 + *z*; ^{iv}: 1/2 – *x*, –1/2 + *y*, 1/2 –*z*

Fungicidal bioassay of intermediate **2** and the target compound **3** against seven phytopathogenic fungi at a concentration of 50 mg/L was compared with commercially pyrimidinamine fungicide diflumetorim and lead compound **YZK-C22** as positive controls. As shown in Table 4, the intermediate **2** showed weak effects at 50 mg/L, the target

compound **3** showed over 50% of inhibitory activities against *B. cinerea*, *C. arachidicola*, *G. zeae*, *R. solani*, *S. sclerotiorum* at 50 mg/L with inhibition of 58%, 53%, 55%, 67% and 59%. Most of them were better than diflumetorim but less than **YZK-C22**. To further assess the fungicidal potency, the EC_{50} values of target compound and positive control**s** with inhibition over 60% at 50 mg/L were measured. The results shown in Table 5 indicated that compound **3** exhibited good fungicidal activities with EC_{50} value of 25.06 mg/L or 60.44 μmol/L against *R. solani*. It was active at the same level of that of the positive control diflumetorim (19.76 mg/L or 60.29 μmol/L) and less active than the positive control **YZK-C22** (4.21 mg/L or 12.32 μmol/L)[16]. Docking studies showed that the target compound had larger binding energy with pyruvate kinase than the positive control **YZK-C22** because of the effecting of absorption, transduction and metabolism. Our studies indicated that isothiazolopurin derivative could be a fungicidal lead deserving for further study.

Table 4. Fungicidal Activities of Compounds Synthesized (Inhibition Rate/%)[a]

Compd.	*A.s*[b]	*B.c*	*C.a*	*G.z*	*P.p*	*R.s*	*S.s*
2	27 ± 0	14 ± 1	43 ± 1	25 ± 2	18 ± 1	24 ± 0	24 ± 1
3	38 ± 1	58 ± 0	53 ± 2	55 ± 1	34 ± 0	67 ± 1	59 ± 2
Diflumetorim	55 ± 1	44 ± 1	67 ± 1	48 ± 1	39 ± 1	74 ± 0	44 ± 2
YZK-C22	60 ± 2	71 ± 3	77 ± 2	77 ± 1	55 ± 2	82 ± 2	63 ± 1

[a] Values are the average of three replicates, tested at a concentration of 50 mg/L.

[b] *A.s*: *Alternariasolani*; *B.c*: *Botrytis cinerea*; *C.a*: *Cercosporaarachidicola*; *G.z*: *Gibberellazeae;* *P.p*: *Physalosporapiricola*; *R.s*: *Rhizoctoniasolani*; *S.s*: *Sclerotinia sclerotiorum.*

Table 5. EC_{50} of the Target Compounds with Inhibition over 60% at 50 mg/L *in Vitro*

Fungi	Compd.	Regression equation	R^2	95% confidence interval(mg/L)	EC_{50} (mg/L)	EC_{50} (μmol/L)
R. solani	**3**	$y = 3.0674 + 1.3814x$	0.9543	17.70~35.47	25.06	60.44
	Diflumetorim	$y = 3.0814 + 1.4806x$	0.9969	18.07~21.61	19.76	60.29
	YZK-C22[16]	$y = 4.2367 + 1.2237x$	0.9766	2.97~5.95	4.21	12.32

Dedicated to the 100th Anniversary of Chemistry at Nankai University

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