Synthesis and Biological Activity of 3-[(6-Chloropyridin-3-yl)methyl]-6-substituted-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-7-imines

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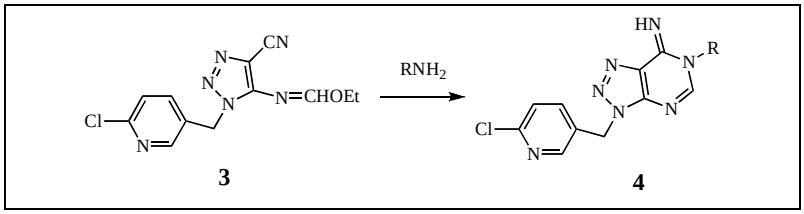

A series of 3-[(6-chloropyridin-3-yl)methyl]-6-substituted-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imines were designed and synthesized *via* a multi-step sequence using 2-chloro-5-(chloromethyl)-pyridine as the starting material. Various primary aliphatic amines, hydrazine and hydrazide reacted with **3** to obtain the cyclization products **4**. Their structures were confirmed by ^{1}H NMR and elemental analyses, some of them were also confirmed by IR, ^{13}C NMR, MS and single crystal X-ray diffraction. The preliminary bioassay indicated that some of the target compounds **4** displayed moderate to weak fungicidal activity and insecticidal activity.

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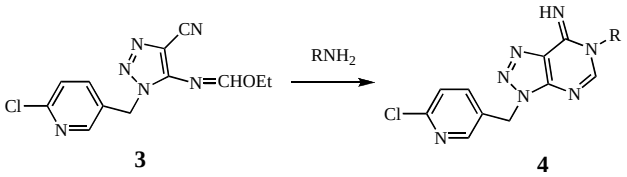
INTRODUCTION

1,2,3-Triazolo[4,5-*d*]pyrimidin-7-one (azaguanines) derivatives have attracted the interest of chemists because of their structural similar with guanines. Some derivatives of them exhibit good pharmaceutical activities such as antitutor, antiviral, and anti-HIV activities [1-5], whereas others exhibit good fungicidal activities [6]. Recently, Ding *et al* reported the synthesis of 1,2,3-triazolo[4,5-*d*]-pyrimidin-7-ones with a phenyl substituted in 3 position *via* Aza-wittig annulation [7], however no biological activities are presented. However, in the study of pharmaceuticals and agrochemicals, the introduction of a pyridyl ring into a parent compound may improve the properties and biological activities of the compounds, and many pyridyl containing compounds are also known to possess a wide range of biological and pharmacological activities, as well as low toxicity toward mammals [8-11]. As a continuation of our ongoing project aimed at investigating novel biologically nitrogen-containing heterocyclic compounds [12,13], we designed and synthesized a series of novel 3-[(6-chloropyridin-3-yl)methyl]-6-substituted-6,7-dihydro-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidin-7-imines (**4**) *via* ethyl *N*-{3-[(6-chloropyridin-3-yl)methyl]-5-cyano-3*H*-1,2,3-triazol-4-yl}formimidate (**3**) annulation with various amines, which have both the skeletons of 1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine and pyridyl ring. Herein, we would like to report the synthesis and biological activity of the title compounds **4** (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

5-(Azidomethyl)-2-chloro-pyridine (**1**) was prepared from the corresponding chloride by treatment with NaN_3 in dry EtOH [14]. The cyclization of **1** with malononitrile in K_2CO_3/DMSO system gave 5-amino-1-[(6-chloro-pyridin-3-yl)methyl]-4-cyano-1*H*-1,2,3-triazole (**2**), which reacted with excess triethyl orthoformate in the presence of a catalytical amount of Ac_2O to obtain **3** in 75% yield. In the synthesis of **3**, we tried to use various catalysts (such as $AlCl_3$, *p*-totuenesulfonic acid and Ac_2O), it was found that only Ac_2O was the more efficient catalyst for the reaction. Various primary aliphatic amines, hydrazine and hydrazides reacted with **3** to obtain the cyclization products **4**. However, as for aromatic amines and sterically hindered aliphatic amines such as *t*-butylamine, reactions did not take place, the electronic and stereo-hindrance effects of amines may play a major role in the cyclization reaction.

The structures of the products were confirmed by ^{1}H NMR and elemental analyses, some of them by IR, ^{13}C NMR, MS and single crystal X-ray diffraction.

The structures of compounds **4** were deduced from their spectroscopic data. In the ^{1}H NMR spectra of **4**, the two methylene protons linking with the pyridyl display a singlet with its chemical shift at δ 5.6-5.8, while the proton in the pyrimidine ring displays a singlet at δ 8.6. The IR spectra of compounds **4** showed normal stretching absorption bands indicating the existence of the N-H, C-N group, no cyano group peak was observed. The EI mass spectra of compounds **4** revealed the existence of their molecular ion peaks and main fragmentation peaks, which were in accordance with the given structures of products.

Moreover, in order to confirm the structures of compounds **4**, a single crystal of the compound **4a** was obtained as colorless crystals from the mixture of dichloromethane and petroleum ether (1:2 *v/v*) and the molecular structure was determined by X-ray diffraction [15].

The preliminary bioassay indicated that some of the target compounds **4** displayed moderate to weak fungicidal activity and insecticidal activity.

Biological activity.

Insecticidal activity. Compounds **4** were tested for insecticidal activities against *aphides* and *tetranychus urticae* at the concentration of 250 mg/L according to a previously reported method [16]. The results of preliminary bioassays also indicated that most of the target compounds did not display good inhibitory activity against *aphides* and *Tetranychus urticae* (see Table 1).

Fungicidal activity. The preliminary fungicidal activities of the target compounds **4** were evaluated by the classic plate method at a concentration of 50 mg/L, which was described in the experimental part. The six fungi used, *Fusarium oxysporium, Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Dothiorella gregaria* and *Colletotrichum gossypi*, belong to the group of field fungi and were isolated from corresponding crops. The activity data were also listed in Table 1. The results indicated that most of compounds **4** exhibit moderate to weak inhibitory activities against the above six fungi, further stucture-activity relationships are under investigation.

In conclusion, a series of 3-[(6-chloropyridin-3-yl)-methyl]-6-substituted-6, 7-dihydro-3*H*-1,2,3-triazolo [4,5-*d*]pyrimidin-7-imines were synthesized in a muti-step sequence. Various primary aliphatic amines, hydrazine and hydrazide reacted with **3** to obtain the cyclization products **4**. However, as for the aromatic amines and sterically hindered aliphatic amines such as *t*-butylamine, reactions did not take place. The preliminary bioassay indicated that some of the target compounds **4** displayed moderate to weak fungicidal activity and insecticidal activity.

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury PLUS400 spectrometer with TMS as the internal reference and DMSO-d6 or $CDCl_3$ as the solvent, while mass spectra were obtained with a Finnigan TRACEMS2000 spectrometer using the EI method. IR spectra were measured by a Nicolet NEXUS470 spectrometer. Elemental analyses were performed with an Elementar Vario ELIII CHNSO elemental analyzer. X-ray diffraction analysis was performed on a Bruker SMART 1000 CCD diffractometer. All of the solvents and materials were reagent grade and purified as required. Compound **1** was prepared according to the reported method [14].

Preparation of 5-Amino-1-[(6-chloropyridin-3-yl) methyl]-4-cyano-1*H*-1,2,3-triazole (2)[16]. The mixture of **1** (8.45 g, 0.05 mol), malononitrile (3.3 g, 0.05 mol), anhydrous K_2CO_3 (20.7 g, 0.15 mol) in DMSO (50 mL) was stirred in 40~50°C until the reaction completed (monitored by TLC, about 1 h). After cooling to r.t., the mixture was poured into a cold H_2O (500 mL), the resulting precipitate was collected by filtration, washed with dry EtOH and Et_2O to obtain **2** as a white solid (11

Table 1

The insecticidal and fungicidal activities of some of compounds **4** (inhibitory rate %)

Compd.	insecticidal activity (250 mg/L)		Fungicidal activity (50 mg/L)					
	apides	*Tetranychus urticae*	*Fusarium oxysporium*	*Rhizoctonia solani*	*Botrytis cinereapers*	*Gibberella zeae*	*Dothiorella gregaria*	*Colletotrichum gossypii*
4a	21.4	10.4	38.1	68.5	58.8	30.4	47.4	52.4
4c	14.3	0.0	39.1	44.1	41.2	4.4	5.3	28.6
4d	21.3	0.0	28.6	64.0	29.4	17.4	5.3	52.4
4e	15.4	12.2	26.09	30.9	11.1	31.3	38.5	14.8
4g	12.5	0.0	30.4	36.1	5.6	15.6	11.5	25.9
4h	13.0	0.0	26.1	30.9	44.4	15.6	0.0	25.9
4i	20.4	0.0	14.3	34.2	11.8	17.4	31.6	47.6
4k	28.3	0.0	34.8	38.1	5.6	34.4	0.0	25.9
4o	24.0	0.0	34.6	63.9	40.7	58.3	50.0	48.2
4r	14.3	22.2	23.1	38.1	55.6	50.0	30.8	48.2
4s	32.1	10.3	26.9	78.3	51.9	63.9	69.2	51.9

g, 94 %), mp 215-216 °; ^{1}H nmr (DMSO-d6): δ 5.47 (s, 2H, CH_2), 7.24 (s, 2H, NH_2), 7.53 (d, *J* = 8 Hz, 1H, Py-H), 7.66 (d, *J* = 8 Hz, 1H, Py-H), 8.38 (s, 1H, Py-H). *Anal*. Calcd. for $C_9H_7ClN_6$: C, 46.07; H, 3.01; N, 35.82. Found: C, 46.23; H, 2.86; N, 35.60.

Preparation of ethyl *N*-{3-[(6-chloropyridin-3-yl)methyl]-5-cyano-3*H*-1,2,3-triazol-4-yl}formimidate (3). A mixture of **2** (2.34 g, 10 mmol), Ac_2O (1 mmol) and triethyl orthoformate (10 mL) was heated to 140ºC, and the ethanol formed was removed. After no EtOH formed, excess triethyl orthoformate was removed under vacum and the residue was purified by flash column chromatography on silica gel using acetone and petroleum ether (1:1 *v/v*) as eluent to give **3** as colorless crystals (2.2 g, 75 %), mp 98-99º; ^{1}H NMR ($CDCl_3$): δ 1.45 (t, *J* = 7.6 Hz, 3 H, CH_3), 4.44 (q, *J* = 8.0 Hz, 2 H, OCH_2), 5.44 (s, 2 H, CH_2), 7.34 (d, *J* = 8 Hz, 1H, Py-H), 7.65 (d, *J* = 8 Hz, 1H, Py-H), 8.43 (s, 1H, Py-H), 8.47 (s, 1H, CH=N). *Anal*. Calcd. for $C_{12}H_{11}ClN_6O$: C, 49.58; H, 3.81; N, 28.91. Found: C, 49.47; H, 3.90; N, 28.75.

General Procedure for the Preparation of 3-[(6-chloropyridin-3-yl)methyl]-6-substituted-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine 4. To the solution of 3 (0.58 g, 2 mmol) in dry CH_3CN (30 mL) was added quickly the appropriate aliphatic amine (or 85% hydrzine or hydrazide, for ammonia gas was pumped) (2 mmol) and the mixture was stirred for at r.t. for 1.5-3 h (monitored by TLC). After the solvent was removed, the resulting precipitate was collected by filtration, washed by dry EtOH and Et_2O, respectively, the target compound 4 was obtained as white crystals (**4a~4u**).

3-[(6-Chloropyridin-3-yl)methyl]-6-isobutyl-6,7-dihydro-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidin-7-imine [15]. (4a) White crystals, yield: 88 %, mp 185-186º; ir: N-H 3253, C-N 1467, 1390 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.97 (d, *J* = 7.6 Hz, 6H, $CH(CH_3)_2$), 2.30-2.34 (m, 1H, $CH(CH_3)_2$), 3.84 (d, *J* = 7.6 Hz, 2H, CH_2), 5.61 (s, 2H, CH_2), 7.32 (d, *J* = 8.0 Hz, 1H, Py-H), 7.72 (d, *J* = 7.6 Hz, 1H, Py-H), 7.75 (s, 1H, Py-H), 8.52 (s, 1H, N=CH); ms: m/z 319 (M+2, 4.08), 318 (M+1, 12.0), 317 (M^+, 13.4), 316 (36.5), 262 (44.8), 232 (82.0), 198 (27.6), 129 (7.1), 126 (100), 90 (28.9). *Anal*. Calcd. for $C_{14}H_{16}ClN_7$: C, 52.91; H, 5.07; N, 30.85. Found: C, 52.74; H, 5.22; N, 30.98.

3-[(6-Chloropyridin-3-yl)methyl]-6-propyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4b). White crystals, yield: 78 %, mp 158-159º; ir: N-H 3247, 1465, C-N 1386 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.99 (t, *J* = 7 Hz, 3H, $CH_2CH_2CH_3$), 1.83-1.87 (m, 2H, $CH_2CH_2CH_3$), 4.02 (t, *J* = 7 Hz, 2H, $CH_2CH_2CH_3$), 5.61 (s, 2H, CH_2), 7.31 (d, *J* = 8.4 Hz, 1H, Py-H), 7.72 (d, *J* = 8 Hz, 1H, Py-H), 7.78 (s, 1H, Py-H), 8.52 (s, 1H, N=CH); ^{13}C nmr (DMSO-d6): δ 10.667, 21.009, 46.311, 47.942, 124.372, 128.424, 130.701, 139.519, 143.787, 149.420, 149.986, 150.495, 152.514. *Anal*. Calcd. for $C_{13}H_{14}ClN_7$: C, 51.40; H, 4.65; N, 32.28. Found: C, 51.58; H, 4.53; N, 32.43.

3-[(6-Chloropyridin-3-yl)methyl]-6-benzyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4c). White crystals, yield: 83 %, mp 207-208º; ir: N-H 3244, C-N 1564, 1465, 1373 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 5.28 (s, 2H, CH_2Ph), 5.60 (s, 2H, CH_2), 7.31-7.36 (m, 6H, Ar-H, Py-H), 7.72 (d, *J* = 8.4 Hz, 1H, Py-H), 7.84 (s, 1H, Py-H), 8.51 (s, 1H, N=CH). *Anal*. Calcd. for $C_{17}H_{14}ClN_7$: C, 58.04; H, 4.01; N, 27.87. Found: C, 57.89; H, 4.20; N, 27.99.

3-[(6-Chloropyridin-3-yl)methyl]-6-[(pyridin-3-yl)methyl]-6,7-dihydro-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidin-7-imine (4d). White crystals, yield: 85 %, mp 191-193º; ^{1}H nmr ($CDCl_3$): δ 5.28 (s, 2H, CH_2Py), 5.60 (s, 2H, CH_2), 7.28-7.33 (m, 2H, Py-H), 7.72-7.79 (m, 2H, Py-H), 7.88 (s, 1H, Py-H), 8.52 (s, 1H, Py-H), 8.58 (d, *J* = 7.6 Hz, 1H, Py-H), 8.67 (s, 1H, N=CH); ms: m/z 354 (M+2, 10.0), 353 (M+1, 35.6), 352 (M^+, 33.2), 351 (M-1, 100), 126 (97.8), 92 (67.1). *Anal*. Calcd. for $C_{16}H_{13}ClN_8$: C, 54.47; H, 3.71; N, 31.76. Found: C, 54.32; H, 3.83; N, 31.60.

3-[(6-Chloropyridin-3-yl)methyl]-6-butyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*] pyrimidin-7-imine (4e). White crystals, yield: 82 %, mp 151-153º; ^{1}H nmr ($CDCl_3$): δ 0.96 (t, *J* = 7.6 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.38-1.42 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.79-1.83 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.10 (t, *J* = 7.6 Hz, 2H, $CH_2CH_2CH_2CH_3$), 5.62 (s, 2H, CH_2), 7.32 (d, *J* = 8.0 Hz, 1H, Py-H), 7.73 (d, *J* = 7.6 Hz, 1H, Py-H), 7.79 (s, 1H, Py-H), 8.52 (s, 1H, N=CH); *Anal*. Calcd. for $C_{14}H_{16}ClN_7$: C, 52.91; H, 5.07; N, 30.85. Found: C, 53.04; H, 5.22; N, 30.71.

3-[(6-Chloropyridin-3-yl)methyl)-6-propenyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4f). White crystals, yield: 86 %, mp 139-140º; ^{1}H nmr ($CDCl_3$): δ 4.68 (d, *J* = 8.0 Hz, 2H, $CH_2CH{=}CH_2$), 5.23-5.27 (m, 2H, $CH_2CH{=}CH_2$), 5.61 (s, 2H, CH_2), 5.97-6.03 (m, 1H, $CH_2CH{=}CH_2$), 7.32 (d, *J* = 8.0 Hz, 1H, Py-H), 7.73 (d, *J* = 8.0 Hz, 1H, Py-H), 7.77 (s, 1H, Py-H), 8.52 (s, 1H, N=CH). *Anal*. Calcd. for $C_{13}H_{12}ClN_7$: C, 51.75; H, 4.01; N, 32.49. Found: C, 51.88; H, 3.85; N, 30.82.

3-[(6-Chloropyridin-3-yl)methyl]-6-hydroxyethyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4g). White crystals, yield: 90 %, mp 193-194º; ^{1}H nmr (DMSO-d_6): δ 3.65 (t, *J* = 8.0 Hz, 2H, CH_2CH_2OH), 4.03-4.07 (m, 2H, CH_2CH_2OH), 5.75 (s, 2H, CH_2), 7.53 (d, *J* = 8.4 Hz, 1H, Py-H), 7.78 (d, *J* = 8.0 Hz, 1H, Py-H), 8.12 (s, 1H, Py-H), 8.47 (s, 1H, N=CH). *Anal*. Calcd. for $C_{12}H_{12}ClN_7O$: C, 47.14; H, 3.96; N, 32.07. Found: C, 47.26; H, 4.06; N, 31.95.

3,6-Bis[(6-chloropyridin-3-yl)methyl]-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4h). White crystals, yield: 89 %, mp 197-198º; ^{1}H nmr (DMSO-d_6): δ 5.25 (s, 2H, CH_2), 5.75 (s, 2H, CH_2), 7.47 (d, *J* = 8.4 Hz, 1H, Py-H), 7.52 (d, *J* = 8.4 Hz, 1H, Py-H), 7.79 (d, *J* = 8.4 Hz, 1H, Py-H), 7.88 (d, *J* = 8.0 Hz, 1H, Py-H), 8.48 (s, 1H, Py-H), 8.50 (s, 1H, Py-H) , 8.54 (s, 1H, N=CH). *Anal*. Calcd. for $C_{16}H_{12}Cl_2N_8$: C, 49.63; H, 3.12; N, 28.94. Found: C, 49.47; H, 3.24; N, 29.09.

3-[(6-Chloropyridin-3-yl)methyl]-6-(2-chlorobenzyl)-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4i). White crystals, yield: 90 %, mp 179-181º; ^{1}H nmr ($CDCl_3$): δ 5.36 (s, 2H, CH_2Ar), 5.60 (s, 2H, CH_2), 7.25-7.44 (m, 5H, Ar-H, Py-H), 7.73 (d, *J* = 8.4 Hz, 1H, Py-H), 7.89 (s, 1H, Py-H), 8.52 (s, 1H, N=CH). *Anal*. Calcd. for $C_{17}H_{13}Cl_2N_7$: C, 52.86; H, 3.39; N, 25.39. Found: C, 52.99; H, 3.51; N, 25.54.

3-[(6-Chloropyridin-3-yl)methyl]-6-hexyl-6, 7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4j). White crystals, yield: 84 %, mp 143-145º; ^{1}H nmr ($CDCl_3$): δ 0.87 (t, *J* = 7.6 Hz, 3H, CH_3), 1.26-1.32 (m, 6H, CH_2), 1.79-1.84 (m, 2H, CH_2), 4.04 (t, *J* = 8.0 Hz, 2H, CH_2), 5.61 (s, 2H, CH_2), 7.31 (d, *J* = 8.4 Hz, 1H, Py-H), 7.72 (d, *J* = 7.2 Hz,, 1H, Py-H), 7.77 (s, 1H, Py-H), 8.52 (s, 1H, N=CH). *Anal*. Calcd. for $C_{16}H_{20}ClN_7$: C, 55.57; H, 5.83; N, 28.35. Found: C, 55.42; H, 5.99; N, 28.49.

3-[(6-Chloropyridin-3-yl)methyl]-6-pentyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4k). White crystals, yield: 86 %, mp 134-136º; ^{1}H nmr ($CDCl_3$): δ 0.90 (t, *J* = 7.6 Hz, 3H, CH_3), 1.32-1.36 (m, 4H, CH_2), 1.81-1.84 (m, 2H, CH_2), 4.11 (t, *J* = 8.0 Hz, 2H, CH_2), 5.62 (s, 2H, CH_2), 7.32 (d, *J* = 8.0 Hz, 1H, Py-H), 7.73 (d, *J* = 8.4 Hz, 1H, Py-H), 7.80 (s, 1H, Py-H), 8.52 (s, 1H, N=CH). *Anal*. Calcd. for $C_{15}H_{18}ClN_7$: C, 54.30; H, 5.47; N, 29.55. Found: C, 54.48; H, 5.59; N, 29.69.

3-[(6-Chloropyridin-3-yl)methyl]-6-isopropyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4l). White crystals, yield: 82 %, mp 150-151°; ^{1}H nmr ($CDCl_3$): δ 1.51 (d, *J* = 7.6 Hz, 6H, CH(*CH_3*)$_2$), 1.64-1.68 (m, 1H, *CH*(CH_3)$_2$), 5.64 (s, 2H, CH_2), 7.32 (d, *J* = 8.0 Hz, 1H, Py-H), 7.74 (d, *J* = 8.0 Hz, 1H, Py-H), 7.96 (s, 1H, Py-H), 8.53 (s, 1H, N=CH). *Anal*. Calcd. for $C_{13}H_{14}ClN_7$: C, 51.40; H, 4.65; N, 32.28. Found: C, 51.52; H, 4.81; N, 32.38.

3-[(6-Chloropyridin-3-yl)methyl]-6-(α-phenylethyl)-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4m). White crystals, yield: 87 %, mp 172-173°; ^{1}H nmr ($CDCl_3$): δ 1.86 (d, *J* = 7.6 Hz, 6H, CH*CH_3*), 4.14-4.18 (m, 1H, *CH*CH_3), 5.64 (s, 2H, CH_2), 7.31-7.42 (m, 6H, Ar-H, Py-H), 7.73 (d, *J* = 8.0 Hz, 1H, Py-H), 7.75 (s, 1H, Py-H), 8.53 (s, 1H, N=CH). *Anal*. Calcd. for $C_{18}H_{16}ClN_7$: C, 59.10; H, 4.41; N, 26.80. Found: C, 58.97; H, 4.29; N, 26.64.

3-[(6-Chloropyridin-3-yl)methyl]-6-methyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4n). White crystals, yield: 84 %, mp 163-164°; ^{1}H nmr ($CDCl_3$): δ 3.57 (s, 6H, CH_3), 5.61 (s, 2H, CH_2), 7.30 (d, *J* = 8.4 Hz, 1H, Py-H), 7.71 (d, *J* = 8.0 Hz, 1H, Py-H), 7.80 (s, 1H, Py-H), 8.51 (s, 1H, N=CH). *Anal*. Calcd. for $C_{11}H_{10}ClN_7$: C, 47.92; H, 3.66; N, 35.56. Found: C, 47.77; H, 3.76; N, 35.68.

3-[(6-Chloropyridin-3-yl)methyl]-6-(2,4-dichlorobenzyl)-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4o). White crystals, yield: 89 %, mp 182-183°; ^{1}H NMR ($CDCl_3$): δ 5.31 (s, 2H, *CH_2*Ar), 5.60 (s, 2H, CH_2), 7.22-7.44 (m, 4H, Ar-H, Py-H), 7.73 (d, *J* = 8.0 Hz, 1H, Py-H), 7.92 (s, 1H, Py-H), 8.51 (s, 1H, N=CH). *Anal*. Calcd. for $C_{17}H_{12}Cl_3N_7$: C, 48.54; H, 2.88; N, 23.31. Found: C, 48.41; H, 3.03; N, 23.45.

3-[(6-chloropyridin-3-yl)methyl]-6-(4-methylbenzyl)-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4p). White crystals, yield: 88 %, mp 217-218°; ^{1}H nmr ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 5.21 (s, 2H, *CH_2*Ar), 5.59 (s, 2H, CH_2), 7.16-7.32 (m, 5H, Ar-H, Py-H), 7.71 (d, *J* = 8.4 Hz, 1H, Py-H), 7.81 (s, 1H, Py-H), 8.50 (s, 1H, N=CH). ^{13}C nmr (DMSO-d6): δ 20.595, 46.364, 48.557, 124.391, 127.649, 128.538, 128.922, 130.659, 133.833, 136.660, 139.546, 143.741, 149.458, 150.005, 152.635. *Anal*. Calcd. for $C_{18}H_{16}ClN_7$: C, 59.10; H, 4.41; N, 26.80. Found: C, 59.24; H, 4.59; N, 26.66.

3-[(6-Chloropyridin-3-yl)methyl]-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-7-imine (4q). White crystals, yield: 89 %, mp >280°; ^{1}H nmr (DMSO-d6): δ 5.85 (s, 2H, CH_2), 7.51 (d, *J* = 8.0 Hz, 1H, Py-H), 7.80 (d, *J* = 8.4 Hz, 1H, Py-H), 8.15 (s, 1H, Py-H), 8.33 (s, 1H, N=CH), 8.50 (s, 2H, NH_2). *Anal*. Calcd. for $C_{11}H_{12}ClN_7$: C, 47.57; H, 4.36; N, 35.31. Found: C, 47.42; H, 4.48; N, 35.13.

6-Amino-3-[(6-chloropyridin-3-yl)methyl]-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*] pyrimidin-7-imine (4r). White crystals, yield: 82 %, mp 188-189°; ^{1}H nmr (DMSO-d6): δ 5.69 (s, 2H, NH_2), 5.74 (s, 2H, CH_2), 7.52 (d, *J* = 8.4 Hz, 1H, Py-H), 7.77 (d, *J* = 8.4 Hz, 1H, Py-H), 8.25 (s, 1H, Py-H), 8.29 (s, 1H, NH), 8.33 (s, 1H, N=CH). *Anal*. Calcd. for $C_{10}H_9ClN_8$: C, 43.41; H, 3.28; N, 40.50. Found: C, 43.25; H, 3.41; N, 40.31.

3-[(6-Chloropyridin-3-yl)methyl]-6,7-dihydro-6-phenoxy-acetoamido-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4s). White crystals, yield: 89 %, mp 274-275°; ^{1}H NMR (DMSO-d6): δ 4.7 (s, 2H, *CH_2*OPh), 5.86 (s, 2H, CH_2), 6.97-7.33 (m, 5H, Ar-H), 7.50 (d, *J* = 7.6 Hz, 1H, Py-H), 7.81(d, *J* = 8.4 Hz, 1H, Py-H), 8.40 (s, 1H, Py-H), 8.51 (s, 1H, N=CH), 10.51 (s, 1H, NH), 10.92 (s, 1H, NH=). Ms: m/z 410 (M+1, 3.7), 317 (M^+, 8.7), 316 (100), 137 (6.5), 126 (21.1), 94 (9.6), 77 (9.0), 42 (72.5). *Anal*. Calcd. for $C_{18}H_{15}ClN_8O_2$: C, 52.63; H, 3.68; N, 27.28. Found: C, 52.48; H, 3.85; N, 27.14.

6-Benzamido-3-[(6-chloropyridin-3-yl)methyl]-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4t). White crystals, yield: 84 %, mp 276-278°; ^{1}H nmr (DMSO-d6): δ 5.84 (s, 2H, CH_2), 7.50-7.85 (m, 5H, Ar-H), 7.88 (d, *J* = 7.6 Hz, 1H, Py-H), 7.94 (d, *J* = 8.4 Hz, 1H, Py-H), 8.01 (s, 1H, Py-H), 8.54 (s, 1H, N=CH); ms: m/z 381 (M+1, 11.6), 380 (M^+, 36.9), 106 (80.6), 105 (100), 77 (10.8). *Anal*. Calcd. for $C_{17}H_{13}ClN_8O$: C, 52.62; H, 3.44; N, 29.43. Found: C, 52.44; H, 3.61; N, 29.55.

6-acetoamido-3-[(6-chloropyridin-3-yl)methyl]-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-imine (4u). White crystals, yield: 82 %, mp 232-234°; ^{1}H nmr (DMSO-d_6): δ 1.96 (s, 3H, CH_3), 5.86 (s, 2H, CH_2), 7.51 (d, *J* = 8.0 Hz, 1H, Py-H), 7.81 (d, *J* = 8.0 Hz, 1H, Py-H), 8.44 (s, 1H, Py-H), 8.53 (s, 1H, N=CH), 10.14 (s, 1H, NHCO), 10.53 (s, 1H, NH=); ms: m/z 319 (M+1, 7.6), 318 (M^+, 17.4), 275 (100), 126 (33.9), 125 (24.6), 43 (14.6). *Anal*. Calcd. for $C_{12}H_{11}ClN_8O$: C, 45.22; H, 3.48; N, 35.16. Found: C, 45.08; H, 3.59; N, 35.02.

Fungicidal activity testing. The fungicidal activity measurement method was adapted from the one described by Molina Torres *et al*. [18]. The synthesized target compounds were dissolved in 0.5-1.0 mL of DMF to the concentration of 500 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50 °C. The mixtures were poured into Petri dishes. After the dished were cooled, the solidified plates were incubated with 4 mm mycelium disk, inverted, and incubated at 28 °C for 48 h. Water was used as the blank control. Three replicates of each test were carried out. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibitory rates were calculated with the following equation: $I = [(C-T)/C] \times 100\%$. Here, *I* is the growth inhibitory rate (%), *T* is the treatment group fungi settlement radius (mm) and *C* is the radius of the blank control. The results are listed in Table 1.

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REFERENCES AND NOTES

[1] Jacobson, K. A.; Daly, J. W.; Manganiello, V. *Purines in Cellular signaling: Targets for New Drugs*, Spinger-Verlag, New York, 1990.

[2] Santana, L.; Teijeira, M.; Uriarte, E.; Balzarini, J.; De Clercq, E. *Eur. J. Med. Chem*. **2002**, *37*, 755.

[3] Blanco, J. M.; Caamano, O.; Fernandez, F.; Garcia-Mera, X.; Hergueta, A. R.; Lopez, C.; Rodriguez-Borges, J. E.; Balzarini, J.; De Clerco, E. *Chem. Pharm. Bull*. **1999**, *47*, 1314.

[4] Nieto, M. I.; Caamano, O.; Fernandez, F.; Gomez, M.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides Nucleic Acids*. **2002**, *21*, 243.

[5] Grifantini, M.; Franchetti, P.; Cappellacci, L.; La Colla, P.; Loi, A.G.; Piras, G. PCT Patent 9,609,307, 1996; *Chem. Abstr*. **1980**, *94*, 165711m.

[6] Nielsen, F. E.; Pedersen, E. B.; Begtrup, M. *Liebigs Ann. Chem*. **1984**, 1848.

[7] Zhao, J. F.; Xie, C.; Ding, M. W., He, H. W. *Synthesis*. **2005**, *15*, 2544.

[8] Liu, M. C.; Lin, T. S.; Cory, J. G.; Cory, A. H.; Sartorelli, A. C. *J. Med. Chem.* **1996**, *39*, 2586.
[9] Finkelstein, B. L.; Martz, M. A.; Strock, C. *J. Pestic. Sci.* **1997**, *50*, 319.
[10] Li, G. Y.; Qian, X. H.; Cui, J. N.; Huang, Q. C.; Zhang, R.; Guan, H. *J. Agric. Food Chem.* **2006**, *54*, 125.
[11] Jo, Y. W.; Im, W. B.; Rhee, J. K.; Shim, M. J.; Kim, W. B.; Choi, E. C. *Bioorg. Med. Chem.* **2004**, *12*, 5909.
[12] Luo, Z. G.; Shi, D. Q. *J. Heterocycl. Chem.* **2006**, *43*, 1021.
[13] Chen, X.–B.; Shi, D.–Q.; Zhu, X.–F. *Chin. J. Chem.* **2007**, *25*, 1854.
[14] Wiley, R. H.; Hussung, K. F.; Moffat, J. *J. Org. Chem.* **1956**, *21*, 190.
[15] Chen, X.–B.; Shi, D.–Q. *Acta Cryst.* **2007**, E63, o337.
[16] Kiriyama, K.; Kagabu, S.; Nishimura, K. *J. Pestic. Sci.* **2004**, *29*, 43.
[17] Hoover, J. R. E.; Day, A. R. *J. Amer. Chem. Soc.* **1956**, *78*, 5832.
[18] Molina-Torres, J.; Salazar-Cabrera, C. J.; Armenta-Salinas, C.; Ramirez-Chavez, E. *J. Agric. Food Chem.* **2004**, 52, 4700.