Synthesis, Crystal Structure, Antifungal Activity and Computational Study on 4-(((8-Chloro-3-oxo-[1,2,4]-triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile①

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ABSTRACT 1,2,4-Triazolo[4,3-*a*]pyridine (TP) is a key intermediate in pesticides, materials and medicines. The title compound 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile was synthesized via three steps, and its structure was characterized by ^{1}H NMR, HRMS and X-ray diffraction. Single-crystal X-ray diffraction reveals that it crystallizes in the monoclinic system, space group $P2_1/c$. Four TP molecules in the symmetric unit are linked through the O–H ··O and O–H ··N hydrogen bonding interactions via two H_2O molecules along with two π-π interactions. The preliminary antifungal activity results indicated that the compound TP exhibited good activities. Theoretical calculation was carried out by DFT method using the 6-31G basis set.

Keywords: 1,2,4-triazolo[4,3-*a*]pyridine, synthesis, crystal structure, antifungal activity, DFT;
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1 INTRODUCTION

Nitrogen containing heterocycles, including fused nitrogen linked heterocycles, are key scaffold in many bioactive compounds[1-3]. Pyridine is an important six-membered heterocycle[4-6] found in natural product niacin firstly. Due to its diversity activities, pyridine derivatives also discovered in many synthetic molecules. They exhibited various activities, such as insecticidal[7], antifungal[8-11], herbicidal[12], antimicrobial[13], antiviral[14], anticancer[15] and nematicidal activity[16-19]. On the other hand, 1,2,4-triazole ring is a key antifungal group in drugs or fungicides, such as fluconazole, voriconazole, ketoconazole, propiconazole, flusilazole, difenoconazole, epoxiconazole and so on. 1,2,4-Triazoles also possessed other activities like anticancer[20], anticonvulsant[21], antifungal[22-24], herbicidal[25], anti-inflammatory[26], anti-hyperglycemic activity[27] and so forth. Fused heterocycle often exhibited the two heterocycls' properties. Some references reported that 1,2,4-triazolo[4,3-*a*]pyridine compounds display good bioactivities[28-30]. Thus, this is a good way to synthesize 1,2,4-triazolo[4,3-*a*]pyridines with novel activity.

Herein, the title compound 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile was synthesized. Its structure was confirmed by X-ray diffraction and their antifungal activity was tested. The antifungal activity tests show that it possessed good antifungal activity. The DFT calculation was done to study its SAR.

2 EXPERIMENTAL

2. 1 Instruments

Melting point was determined by an X-4 apparatus and uncorrected. ^{1}H NMR spectra were measured on a Bruker AV-400 instrument using TMS as an internal standard and $CDCl_3$ as the solvent. HRMS was determined on an Agilent

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LC-QTOF instrument. Crystallographic data of the compound were collected on a Rigaku Saturn diffractometer. All the reagents were of analytical grade or freshly prepared before use. The course of the reactions was monitored by TLC; analytical TLC was performed on silica gel GF_{254}.

2. 2 General procedure

2,3-Dichloropyridine (10 mmol) and $NH_2NH_2·H_2O$ (30 mmol) were added into ethanol (80 mL), and then refluxed for three days to give 3-chloro-2-hydrazinylpyridine. N,N′-Carbonyldiimidazole (1 mmol) and 3-chloro-2-hydrazinylpyridine (143 mg, 1 mmol) were dissolved in dried THF (10 mL). After stirring at room temperature for 5 h, the mixture was poured into water, and white solid (**2**) was precomputed. At last, the intermediate 8-chloro-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one (1 mmol) and NaOH (1.1 mmol) were dissolved in DMF (5 mL). Then the mixture was stirred at room temperature for 10 min, followed by the addition of 4-(chloromethyl)benzonitrile (1.1 mmol). The mixture was further stirred at room temperature overnight and poured into ice water, obtaining light yellow solid collected by filtration and recrystallization in ethanol with the yield of 85%. m.p. 216～218 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 5.25(s, 2H, NCH_2), 6.52(t, J = 6.8Hz, 1H, Py-H), 7.20(d, J = 7.2Hz, 1H, Py-H), 7.52(d, J = 8.4Hz, 2H, Ar-H), 7.64(d, J = 8.0Hz, 2H, Ar-H), 7.75(d, J = 6.8Hz, 1H, Py-H). HR-ESI-MS for $C_{14}H_9ClN_4NaO$: calcd. 307.0357$[M+Na]^+$; Found: 307.0360$[M+Na]^+$.

2. 3 Structure determination

A colorless rectangle crystal suitable for X-ray diffraction study was cultivated in the test tube from EtOH by self-volatilization. A crystal with dimensions of 0.24mm × 0.04mm × 0.04mm was mounted on a Rigaku Saturn diffractometer equipped with a graphite-monochromatic Mo$K\alpha$ radiation (λ = 0.71073 Å). Intensity data were collected at 113(2) K by using a multi-scan mode in the range of $2.0 \leqslant \theta \leqslant 27.9°$ with the following index ranges: $-18 \leqslant h \leqslant 18$, $-15 \leqslant k \leqslant 15$ and $-8 \leqslant l \leqslant 8$. A total of 11685 reflections were collected and 2541 were independent (R_{int} = 0.0574), of which 1962 with $I > 2\sigma(I)$ were observed. The crystal structure was solved by direct methods with SHELXS-97[31] and refined by full-matrix least-squares refinements based on F^2 with SHELXL-97. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were located in the calculated positions and refined with a riding model. The final refinement converged at R = 0.0794, wR = 0.2001, $w = 1/[\sigma^2(F_o^2) + (0.0655P)^2 + 7.3623P]$, where $P = (F_o^2 + 2F_c^2)/3$, S = 1.144, $(\Delta/\sigma)_{max}$ = 0.000.

2. 4 Antifungal activity

The antifungal activities of compound 3 were tested *in vitro* against *Gibberella zeae* (GZ), *Fusarium oxysporum* (FO), *Phytophthora infestans* (PI), *Phytophthora capsici* (PC), *Rhizoctonia solani* (RS), *Sclerotinia sclerotiorum* (SS), *Alternaria solani* (AS), *Physalospora piricola* (PP), *Cercospora arachidicola* (CA), and *Botrytis cinerea* (BC). The relative percent inhibition (%) has been determined using the mycelium growth rate method. The inhibition of compound 3 compared to the blank assay was calculated via the following equation:

inhibition (%) = $(CK\text{-}CI)/CK \times 100\%$

where CK is the average diameter of mycelia in the blank test and CI is the average diameter of mycelia in the presence of those compounds. All experiments were replicated three times.

2. 5 Computational methods

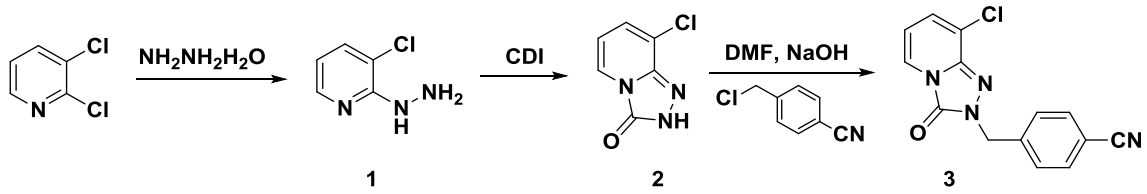
The crystal structure of 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile was selected as the initial structure and optimized using B3LYP/6-31G methods in Gaussian 03 package[32]. All the convergent precisions were the system default values, and all the calculations were carried out on the DELL computer.

3 RESULTS AND DISCUSSION

3. 1 Synthesis and spectra analysis

The synthesis route of 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile is outlined in Scheme **1**. Many references reported the synthesis methods about triazolone[33, 34]. The general method is using phosgene as cyclization reagent. In this paper, 8-chloro-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one was synthesized by using CDI as green cyclization reagent, due to its high reactivity, environmental friendly, higher yields and separate easily. Then the key intermediate 8-chloro-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one reacted with 4-(chloromethyl)benzonitrile under NaOH in DMF to give final product in excellent yield. The solid was collected by filtered, dried, and recrystallized from EtOH to afford light yellow product, yield 85%. The structure of compound 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)-thio)methyl)benzonitrile **3** was determined by ^{1}H NMR, and high resolution mass spectroscopy. From ^{1}H NMR data, the

three proton signals of pyridine ring were found at 6.52, 7.20, 7.75 ppm, respectively. The $-NCH_2$ protons was appeared at 5.25 ppm. The protons of benzene ring are assigned at 7.52 ppm and 7.64 ppm as two doublets. The high resolution mass result of 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile indicated it is agreement with the calculated value.



1 2 3

Scheme 1. Synthetic route of 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile

3. 2 Crystal structure

Some representative bond angles and bond distances of 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)-thio)methyl)benzonitrile **3** are listed in Table 1. The molecular structure and packing diagram of 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile is illustrated in Figs. 1 and 2, respectively. The optimized parameters based on B3LYP/6-31G set for the compound 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)thio)methyl)benzonitrile **3** are also given in Table 1. From Table 1, the theoretical bond angles and bond lengths were a little different from the experimental data.

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

Bond	Dist.	DFT	Angle	(°)	DFT
N(1)–C(6)	1.390(6)	1.43462	C(5)–N(1)–C(6)	108.2(4)	105.13096
N(3)–C(6)	1.368(6)	1.47629	C(5)–N(1)–C(1)	123.3(4)	122.18059
N(2)–N(3)	1.383(6)	1.40147	C(6)–N(1)–C(1)	128.5(4)	132.67808
N(2)–C(5)	1.316(6)	1.31740	C(6)–N(3)–N(2)	114.2(4)	108.27013
N(1)–C(1)	1.389(6)	1.36927	C(6)–N(3)–C(7)	126.0(4)	125.86494
C(6)–O(1)	1.224(6)	1.20800	N(3)–C(7)–C(8)	112.6(4)	109.49999
N(3)–C(7)	1.456(6)	1.45000	O(1)–C(6)–N(3)	130.2(5)	127.60941
C(7)–C(8)	1.513(7)	1.49700	N(3)–C(6)–N(1)	102.5(4)	104.78114
N(1)–C(5)	1.385(6)	1.38383	C(4)–C(3)–C(2)	120.1(5)	122.50776
C(11)–C(14)	1.440(8)	1.31300	C(3)–C(4)–Cl(1)	124.1(4)	122.16483
C(14)–N(4)	1.146(7)	1.15800	N(4)–C(14)–C(11)	178.0(6)	180.00000

The general bond angles and bond lengths of ring systems (pyridine ring, 1,2,4-triazole ring and phenyl ring) were in normal ranges. The N(1)–C(1) (1.389(6) Å), N(1)–C(6) (1.390(6) Å), N(2)–C(5) (1.316(6) Å) and N(1)–C(5) (1.385(6) Å) bonds were longer than the normal C= N (1.27 Å) [35], which indicated electron delocalized on pyridine ring and 1,2,4-triazole ring. The bond lengths of C(14)–N(4) and C(6)–O(1) are 1.146(7) and 1.224(6) Å, which are according to the cycan group and the carbonyl group. The bond angles of N(3)–C(7)–C(8) and N(4)–C(14)–C(11) were 112.6(4)° and 178.0(6)°, respectively. The torsion angles of C(6)–N(3)–C(7)–C(8) and N(2)–N(3)–C(7)–C(8) were –95.9(5)° and 77.0(5)°, respectively, which indicated that 1,2,4-triazolo[4,3-*a*]pyridine ring is nearly vertical with the benzene ring. As shown in Fig. 1, the phenyl ring (C(8)～C(13)) is vertical with 1,2,4-triazolo[4,3-*a*]pyridine ring (N(2), N(3), C(6), N(1), C(1), C(2), C(3), C(4), C(5)), which dihedral angle (θ) is 95.5° with plane equation $-1.936x + 12.952y - 1.479z = 10.2718$ and $-8.102x + 0.445y + 6.628z = -6.6638$ respectively, and the largest deviation from the least-squares plane is 0.0067 and 0.0079 nm.

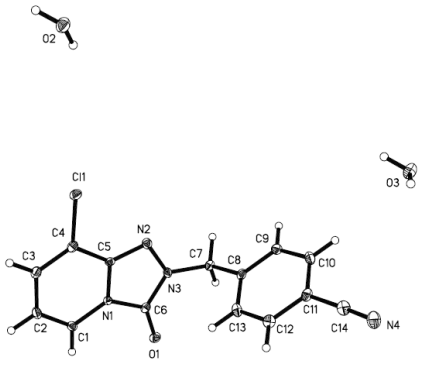


Fig. 1. Molecular structure of the title compound

Compound 4-(((8-chloro-3-oxo-[1,2,4]triazolo[4,3-*a*]pyridine-2(3*H*)-yl)thio)methyl)benzonitrile had intermolecular hydrogen bonds via two water molecules. The parameters of hydrogen bonds are given in Table 2. They are linked together by O–H ··N and O–H ··O. In the *bc* plane, they are linked together by O–H ··O and O–H ··N hydrogen bonds (Fig. 2). There is also intermolecular face-to-face π-π stacking between the two benzene rings and two 1,2,4-triazolo[4,3-*a*]pyridine rings in the crystal. It is worth noting that the two molecules of benzene ring-benzene ring and 1,2,4-triazolo[4,3-*a*]pyridine ring-1,2,4-triazolo[4,3-*a*]pyridine ring were centrosymmetric, with their centroid distances to be 3.771 and 3.630 Å, respectively. These hydrogen bonding interactions and π-π stacking formed an infinite one-dimensional chain structure.

Table 2. Hydrogen Bonds of Compound 3

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
O(2)–H(2A)···O(3)#1	0.87	1.91	2.762(6)	169
O(2)–H(2B)···O(1)#2	0.86	1.97	2.822(6)	173
O(3)–H(3A)···N(4)#3	0.86	2.14	2.963(7)	161
O(3)–H(3B)···O(2)#4	0.88	1.8	2.754(7)	178

Symmetry codes: #1: –*x*+1, –*y*+1, –*z*; #2: *x*, *y*–1, *z*; #3: *x*, –*y*+3/2, *z*–1/2; #4: –*x*+1, *y*+1/2, –*z*+1/2

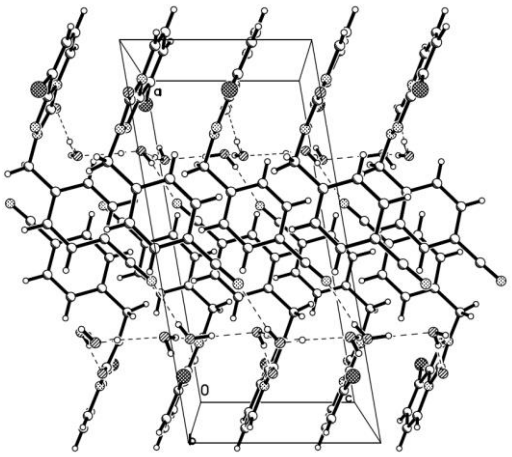


Fig. 2. A view of the packing molecule in the *ac* and *bc* planes

3. 3 Antifungal activity

The antifungal activities of compound **3** are listed in Table 3, showing its good antifungal activity. Among the ten fungi, compound **3** exhibited the best activity against *Phytophthora infestans* (91.2%). It also displayed good inhibition against *Physalospora piricola* (81.0%) and *Cercospora arachidicola* (82.5%). For the other seven fungi, this compound exhibited moderate acitivity (46%～72%).

Table 3. Antifungal Activity of Compound 3 against Ten Fungi at 50 ppm

No.	FO	PP	CA	AS	GZ	PC	PI	SS	BC	RS
3	55.6	81.0	82.5	72.7	46.2	57.1	91.2	69.2	64.5	57.1

3. 4 Frontier molecular orbital (FMO) energy analysis and molecular total energies

The energy of FMO was calculated using DFT method and the results are listed in Table 4. According to the frontier molecular orbital theory, LUMO can accept electrons first, while HOMO can provide electrons[36, 37]. Thus, the HOMO and LUMO give the information of electronic transport. From Fig. 3, the geometry of compound **3** was optimized using DFT method with B3LYP/6-31G set. The HOMO of compound **3** is mainly located on the benzene ring, CH_2 group and 1,2,4-triazolo[4,3-*a*]pyridine ring, except CN group, while LUMO is only located on the 1,2,4-triazolo[4,3-*a*]pyridine ring and a few CH_2 group. From Fig. 3, the electron transits from the phenyl ring to 1,2,4-triazolo[4,3-*a*]pyridine ring via CH_2 group with the energy gap to be 0.14934 Hartree.

Table 4. Total Energy and Frontier Orbital Energy

Energy	DFT
E_{total}/Hartree[b]	–1292.99315692
E_{HOMO}/Hartree	–0.21690
E_{LUMO}/Hartree	–0.06756
ΔE[a]/Hartree	0.14934

[a] $\Delta E = E_{LUMO} - E_{HOMO}$; [b] 1 Hartree = 4.35974417 × 10^{-18}, J = 27.2113845 ev

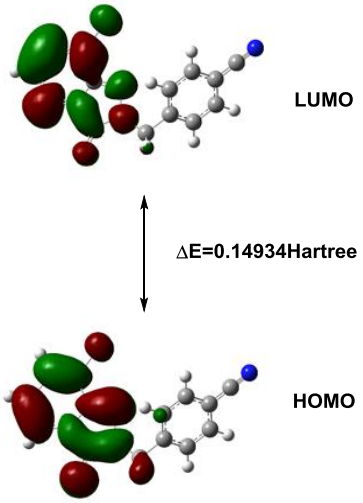


Fig. 3. LUMO, HOMO and energy gap of compound 3

3. 5 Mulliken atomic charges and ESP

The Mulliken atomic charges are calculated and the results are listed in Table 5. The Electrostatic potential (ESP) map is shown in Fig. 4, in which the most negative atoms are focused on the nitrogen atoms of 1,2,4-triazolo[4,3-*a*]pyridine ring and cycan group and the oxygen atom of carbonyl group, which can accept electrons firstly. Therefore, good antifungal activity was possessed, which may be due to the interaction of amino acid residue of fungi with the nitrogen atoms of 1,2,4-triazolo[4,3-*a*]pyridine ring and cycan group and the oxygen atom of carbonyl group.

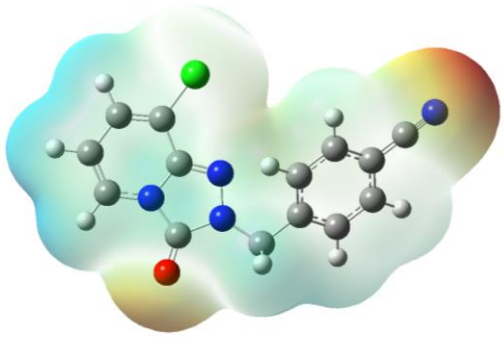


Fig. 4. Electrostatic potential mapping on the electron density (isovalue = 0.04)

Table 5. Mulliken Atomic Charges of Compound 3 Except for Atoms H (e)

Atom	DFT	Atom	DFT	Atom	DFT
O(1)	–0.402	C(2)	–0.155	C(9)	0.080
Cl(1)	0.221	C(3)	–0.124	C(10)	0.105
N(1)	–0.751	C(4)	–0.251	C(11)	0.165
N(2)	–0.258	C(5)	0.514	C(12)	0.087
N(3)	–0.521	C(6)	0.720	C(13)	0.163
N(4)	–0.190	C(7)	–0.125	C(14)	–0.191
C(1)	0.164	C(8)	0.072		

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