Synthesis of Two 1,3,4-thiadiazole Compounds: Crystal Structure, Theoretical and Antifungal Activity Study

[1]Qiao Wang, [1]Zhong-Hua Shen, [1]Zhao-Hui Sun, [1]Jian-Quan Weng, [1]Cheng-Xia Tan
[1]Xing-Hai Liu* and [2]Yong-Gang Zhang**
[1]College of Chemical Engineering, Zhejiang University of Technology,
Hangzhou 310014, Zhejiang, China.
[2]Biology Institute of Shandong Academy of Science, Jinan, 250014, China.
xhliu@zjut.edu.cn*; zhangyg@sdas.org**

(Received on 16th January 2017, accepted in revised form 6th July 2017)

Summary: Two novel 1,3,4-thiadiazole compounds, $C_{15}H_{10}N_4S_2$ (**5a**) and $C_{18}H_{19}N_3S_2$ (**5b**) were designed and synthesized by reactions of key intermediate 5-(pyridin-4-yl)-1,3,4-thiadiazole-2-thiol and two substituted benzyl chloride (4-*t*-Bu and 3-CN). The two 1,3,4-thiadiazole structures were confirmed by ^{1}H-NMR, MS , elemental analyses and X-Ray diffraction. Compound **5a** is triclinic with space group *P*-1 and cell constants: a = 6.1426 (7), b = 8.5323 (14), c = 13.840 (2) Å, α = 90.199 (12), β = 90.002 (11), γ =106.762 (13)°, Dc = 1.484 g/cm^3, Z = 2, V = 694.52 (17) Å^3, the final R = 0.0400 and wR = 0.111 for 1786 observed reflections with $I > 2\sigma(I)$. Compound **5b** is triclinic with space group *P2(1)/c* and cell constants: a = 10.490 (5), b = 19.818 (10), c = 8.825(5) Å, α = 90, β = 98.989(10), γ =90°, Dc = 1.252 g/cm^3, Z = 4, V = 1812.2(16) Å^3, the final R = 0.0630 and wR = 0.192 for 2023 observed reflections with $I > 2\sigma(I)$. Theoretical calculation was carried out by DFT method using 6-31G basis set. The compounds also possessed moderate fungicidal activity.

Keywords: Synthesis, 1,3,4-thiadiazole, Pyridine, Fungicidal activities, Crystal structure, DFT

Introduction

In recent years, heterocycles contain nitrogen and sulfur atoms received considerable attentions because of their biological importance [1-5]. Thiadiazole derivatives possess diversity biological activities, such as antifungal activity [6-8], antiproliferative activity [9], anticancer activity [10], antitubercular activity [11], antibacterial activity [12], and (COX-2) inhibitors [13]. On the other hand, pyridine derivatives exhibited widely biological activities, such as herbicidal activity [14, 15], antifungal activity [16, 17], antitumor activity [18], and antimicrobial activity [19].

As continuate our work on the find drug lead compounds[20-23], the title two compound (3-(((5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl)thio)methyl)benzonitrile and 2-((4-(tert-butyl)benzyl)thio)-5-(pyridin-4-yl)-1,3,4-thiadiazole) were designed by link pyridine and 1,3,4-thiadiazole heterocycle. Two new 1,3,4-thiadiazole derivatives were synthesized and determined by ^{1}H-NMR, ESI-MS and elemental analysis. The crystal structures of two thiadiazole compounds were analyzed using X-ray diffraction method. The antifungal activities of the two compounds were tested.

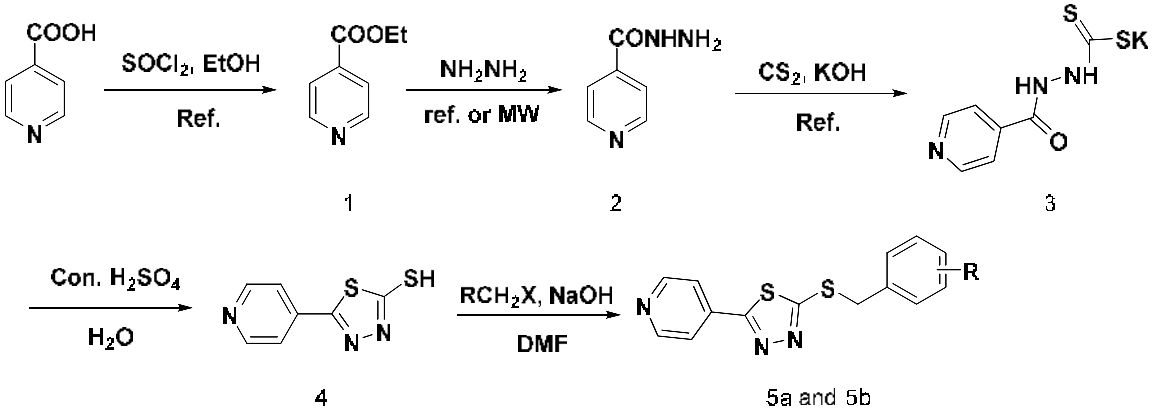
Experimental

Instruments

Melting points were determined using 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 $CDCl_3$ asa 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.

---

[*]To whom all correspondence should be addressed.



Scheme-1: The synthetic route of title compounds

Synthesis of compound **5**

The synthetic route of 3-(((5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl)thio)methyl) benzonitrile was shown in Scheme **1**. The intermediate ethyl isonicotinate, isonicotinyi hydrazine, potassium-pyridine-dithiocarbazate, 5-(pyridin-4-yl)-1,3,4-thiadiazole-2-thiol was synthesized according to our previous work [24]. DMF (5 mL), **4** (0.25 g, 1 mmol), 3-(chloromethyl)benzonitrile or 1-(*tert*-butyl)-4-(chloromethyl)benzene (1.1 mmol) and NaOH (0.05 g, 1.2 mmol) was placed in a CEM designed 10 mL pressure-rated vial. The mixture was irradiated in a CEM Discover Focused Synthesizer (150 w, 90°C, 200 psi, 15 minutes). The mixture was cooled to room temperature by passing compressed air through the microwave cavity. Then the mixture poured into cold ice (40 mL) and the title compound was filtered. The crude product was recrystallized from EtOH to give the title compound **5a** and **5b.** Compound **5a** with yield 84%, m.p.169-172℃; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 4.68 (s, 2H, SCH_2), 7.48 (s, 1H, ArH), 7.60 (s, 1H, ArH), 7.76-7.81 (m, 4H, ArH and Py), 8.80 (s, 2H, Py). ESI-MS: 311 $[M+H]^+$; Anal. calcd. For $C_{15}H_{10}N_4S_2$: C, 58.04; H, 3.25; N, 18.05; found: C 58.16, H 3.33, N 18.24; Compound **5b** with yield 90%, m.p.161-163℃; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 1.31(s, 9H, Bu), 4.64(s, 2H, SCH_2), 7.40(q, J = 8.6 Hz, 4H, ArH), 7.78(d, J = 5.8 Hz, 2H, Py), 8.77(d, J = 5.5 Hz, 2H, Py). ESI-MS: 342$[M+1]^+$; Anal. calcd. For $C_{18}H_{19}N_3S_2$: C, 63.31; H, 5.61; N, 12.30; found: C 63.52, H 5.77, N 12.46.

Theoretical Calculations

According to the above crystal structure, a crystal unit was selected as the initial structure, while B3LYP/6-31G (d,p) methods in Gaussian 03 package[25] were used to optimize the structure of the title compound. All the convergent precisions were the system default values, and all the calculations were carried out on the DELL computer.

Structure Determination

A colorless crystal suitable for X-ray diffraction study was cultivated in the test tube from EtOH by self-volatilization. A crystal with dimensions of 0.20mm × 0.18mm × 0.10mm 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 293 (2) K by using a multi-scan mode in the range of $2.9° \leq \theta \leq 26.3°$ with the following index ranges: $-7 \leq h \leq 7$, $-9 \leq k \leq 10$ and $-17 \leq l \leq 16$. A total of 3151 reflections were collected and 2306 were independent (R_{int} = 0.018), of which 1786 with $I > 2\sigma(I)$ were observed. The crystal structure was solved by direct methods with SHELXS-97 [26] 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 = 0.04, wR = 0.111, $w = 1/[\sigma^2(F_o^2) + (0.0587P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$, S = 1.01, $(\Delta/\sigma)_{\max} = 0.2$.

Table-3: Crystal Structure and Data Refinement Parameters.

Compounds	5a	5b
Empirical Formula	$C_{15}H_{10}N_4S_2$	$C_{18}H_{19}N_4S_2$
Color/shape	colorless / rectangle	colorless/block
Formula Weight	310.39	341.48
Crystal System / Space Group	Triclinic, P1	Monoclinic, P2(1)/c
a / Å	6.1426(7)	10.490(5)
b / Å	8.5323(14)	19.818(10)
c / Å	13.840(2)	8.825(5)
α / °	90.199(12)	90
β / °	90.002(11)	98.989(10)
γ / °	106.762(13)	90
V / Å^3	694.52(17)	1812.2(16)
Z	2	4
D_{calc} (g/cm^3)	1.484	1.252
μ (mm^{-1})	0.3800	0. 296
Crystal size (mm)	0.56 × 0.20 × 0.19	0.20 × 0.18 × 0.12
F(000)	320	720
Temp (K)	293(2)	113(2)
Theta range for collection	2.9–26.3°	1.9-27.1°
Reflections collected	3151	21851
Independent reflections	2306	3720
Data/restraints/parameters	3720 / 0 / 237	3980 / 0 / 211
Goodness of fit on F^2	1.077	1.041
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0335, wR2 = 0.0882	R1 = 0.0628, wR2 = 0.1609
R indices (all data)	R1 = 0.0413, wR2 = 0.0924	R1 = 0.0958, wR2 = 0.1921
Largest difference peak/hole	0.294 and -0.369	0.377 and -0.331

Antifungal Activity

Antifungal activities of compound **5a** and **5b** against *Stemphylium lycopersici*(SL), *Fusarium oxysporum* (FO) and *Botrytis cinerea*(BC) were evaluated at 500 μg/mL according to our previous references [27] and the results are listed in Table-4. The results showed that the two compound exhibited good activity against *Stemphylium lycopersici.* Meanwhile, the two compounds possessed moderate activity against *Fusarium oxysporum*. But they almost held no inhibitory against *Botrytis cinerea.*

Table-4: The antifungal activity of compound 5a and 5b at 500 μg/mL.

No.	SL	FO	BC
5a	69.05%	72.22%	21.30%
5b	75.30%	63.33%	11.11%
Control	59.58%	81.69%	45.56%

Note: Control for SL: Zhongshengmycin; Control for FO: Thiophanate-Methyl; Control for BC: Cyprodinil

Results and Discussion

Synthesis and Spectra

The synthesis pathway of the two 1,3,4-thiadiazole compounds is depicted in Scheme **1**. It is reported that there are many synthesis methods for 1,3,4-thiadiazoles[6,7]. In this paper, we also use microwave irradiation method to synthesis of title compound, due to its short reaction time, higher yields and environmental friendly. The key intermediate 5-(pyridin-4-yl)-1,3,4-thiadiazole-2-thiol(4) and substituted benzyl chloride took place smoothly under NaOH in DMF in microwave reactor resulted in the formation of final product in excellent yield. The separated solid was washed with water and followed by filtered, dried, and crystallized from EtOH to furnish analytically pure white yellow product, yield 84%.

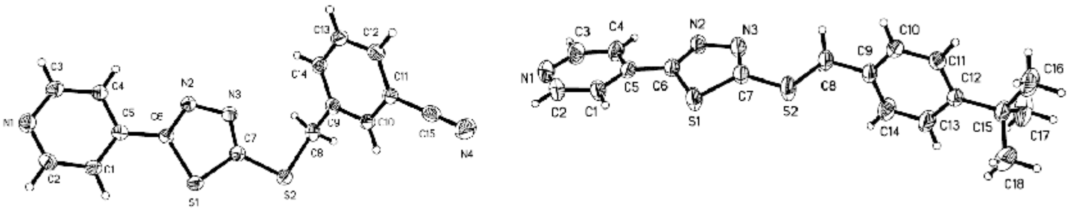
The structures of compound **5a** and **5b** were determined by ^{1}H-NMR and Mass sepctrocopy. From the ^{1}H-NMR data, the appearance of signals at 8.77-8.80, 7.76-7.81，7.40-7.60 ppm are assigned to two aromatic protons (Pyridine ring and Phenyl ring). The $-SCH_2$ protons is found at 4.68 and 4.64 ppm, respectively. The mass and elemental analysis results of two thiadiazole compounds indicated they are agreement with the calculated value.

Crystal Structure

Some representative bond angles and bond distances of compound 5a and 5b are listed in Table-1. The molecular structures and packing diagram of 5a and 5b are illustrated in Fig. 1 and Fig. 2 respectively. The optimized parameters based on B3LYP/6-31G set for the two thiadiazole compounds are 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 **5a** and **5b.**

Bond for 5a	Dist.	DFT	Angle for 5a	(°)	DFT
S(1)-C(6)	1.733(2)	1.84180	C(6)-S(1)-C(7)	86.96(12)	84.66548
S(1)-C(7)	1.724(3)	1.81974	C(7)-S(2)-C(8)	100.08(12)	99.75205
S(2)-C(7)	1.746(3)	1.79918	C(2)-N(1)-C(3)	115.4(3)	117.47651
S(2)-C(8)	1.820(3)	1.94141	C(6)-N(2)-N(3)	113.2(2)	114.49690
N(1)-C(2)	1.328(3)	1.35115	C(7)-N(3)-N(2)	111.9(2)	113.72381
N(1)-C(3)	1.341(3)	1.35408	S(2)-C(7)-N(3)	124.6(2)	125.74802
N(2)-C(6)	1.302(3)	1.30997	N(4)-C(15)-C(11)	179.0(3)	179.97727
N(2)-N(3)	1.380(3)	1.39528	N(1)-C(2)-C(1)	124.5(3)	123.23807
N(3)-C(7)	1.304(3)	1.31088	C(4)-C(5)-C(6)	120.2(2)	119.59514
N(4)-C(15)	1.137(3)	1.17430	N(2)-C(6)-C(5)	122.2(2)	124.06537
C(1)-C(2)	1.376(4)	1.39633	S(1)-C(7)-S(2)	120.93(14)	120.11378
C(1)-C(5)	1.389(3)	1.40559	C(9)-C(8)-S(2)	114.19(17)	113.83326
Bond for 5b	**Dist.**	**DFT**	**Angle for 5b**	**(°)**	**DFT**
S(2)-C(7)	1.741(3)	1.79725	C(7)-S(2)-C(8)	101.51(12)	98.93662
S(2)-C(8)	1.816(3)	1.94725	C(7)-S(1)-C(6)	87.41(13)	84.57427
S(1)-C(7)	1.733(3)	1.82407	C(6)-N(2)-N(3)	113.0(2)	113.05036
S(1)-C(6)	1.736(3)	1.84125	N(2)-C(6)-C(5)	123.8(2)	123.95467
N(2)-C(6)	1.305(3)	1.31002	N(2)-C(6)-S(1)	113.41(19)	114.14026
N(2)-N(3)	1.397(3)	1.39499	C(5)-C(6)-S(1)	122.81(19)	122.99495
C(6)-C(5)	1.475(3)	1.45974	C(7)-N(3)-N(2)	112.1(2)	113.61248
N(3)-C(7)	1.304(3)	1.31172	C(1)-C(5)-C(4)	117.6(2)	117.88270
C(5)-C(1)	1.372(4)	1.40939	C(1)-C(5)-C(6)	122.1(2)	122.49750
C(5)-C(4)	1.398(4)	1.40569	C(4)-C(5)-C(6)	120.3(2)	119.61980
C(10)-C(9)	1.371(3)	1.40619	C(9)-C(10)-C(11)	121.6(2)	120.75263
C(10)-C(11)	1.379(3)	1.39433	C(10)-C(9)-C(14)	117.1(2)	120.96394
C(9)-C(14)	1.387(3)	1.40268	C(2)-N(1)-C(3)	115.6(3)	117.40718
C(9)-C(8)	1.513(3)	1.49669	S(1)-C(7)-S(2)	120.08(15)	120.79959
N(1)-C(2)	1.328(4)	1.35124	N(3)-C(7)-S(2)	125.8(2)	125.06012
N(1)-C(3)	1.330(4)	1.35432	C(14)-C(9)-C(8)	121.2(2)	120.96433
C(1)-C(2)	1.397(4)	1.39378	C(9)-C(8)-S(2)	107.47(18)	108.83123
C(12)-C(13)	1.410(4)	1.41006	N(3)-C(7)-S(1)	114.02(19)	114.14026
C(12)-C(15)	1.516(3)	1.54304	N(1)-C(2)-C(1)	124.4(3)	123.41410



5a **5b**

Fig. 1: The crystal structure of compound **5a** and **5b.**

The genergal bond angles and bond lengths of ring system (pyridine ring, phenyl ring and 1,3,4-thiadiazole ring) were in normal ranges [28-30]. The N1-C2 [1.328(3) Å, 5a and 5b], N2-C6 [1.302(3) Å, (5a); 1.305(3) Å, (5b)], N3-C7 [1.304(3) Å, 5a and 5b] bond were longer than the general C=N(1.27 Å) double bond length [33], which indicated electron delocalization in the pyridine ring and 1,3,4-thiadiazole ring. The bond angles of C7-S2-C8(5a) and S2-C8-C9(5a) were 100.08(12) and 114.19(17)° respectively, meanwhile, for the compound 5b, the C6-S1-C7 and C7-S2-C8 are 101.51(12) and 87.41(13) respectively. The torsion angle of thioether group C7–S2–C8–C9 was 79.9(2)°. The torsion angle of compound 5b is different with the compound 5a. The torsion angle of thioether group C7–S2–C8–C9 is -174.15(18)°. It indicated that benzene ring is nearly parallel with the 1,3,4-thaidiazole ring. On the opposite, the phenyl ring was nearly vertical with the 1,3,4-thiadiazole with a angle (θ) of 71.9° for compound 5a. The 1,3,4-thiadiazole ring was fairly planar with pyridine ring with angle (θ) of 1.2° and 12.0°. From Fig. 2a, the intermolecular face-to-face π-π stacking can be found in the compound 5a. It is worth mention that the two molecules of thiadiazole ring-thiadiazole ring, thiadiazole ring-pyridine ring, and phenyl rings were centrosymmetric: the centroid distance of thiadiazole ring-thiadiazole ring, thiadiazole ring-pyridine ring, and phenyl rings were 3.574 Å, 3.790 Å and 3.778 Å, respectively. As well as compound 5a, we can found two edge-to-face π-π stacking pattern of compound 5b (Fig. 2b), it is worth mention that each stacking between the CH and phenyl ring(C9~C14): the centroid separation of them is 3.492 Å and 3.499 Å respectively, and their dihedral angle is 77.03° and 53°. These π-π stacking interactions play an important factor in stabilizing the two thiadiazole crystal structure.

.

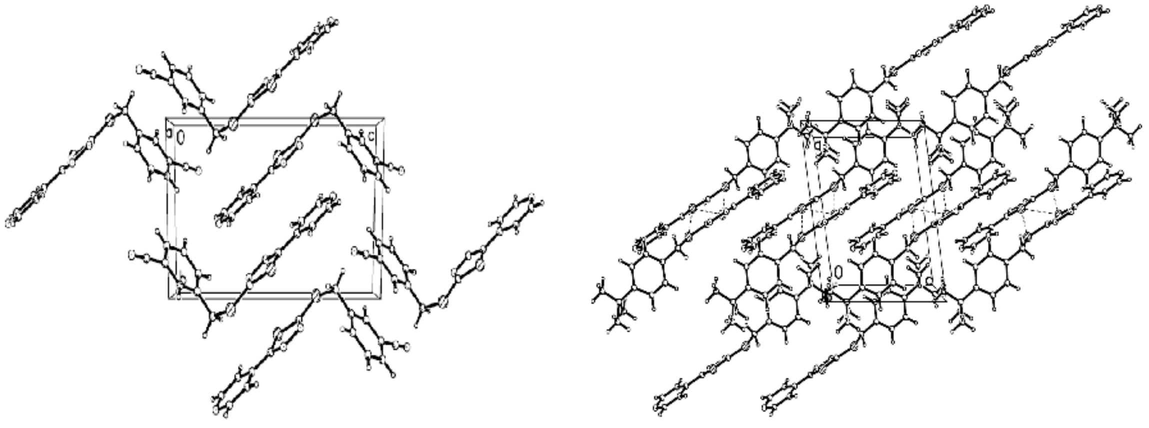


Fig. 2: A view of pack molecule **1** and **2**.

In Table-1, we can see the bond lengths and the bond angles, whatever the calculated value or the experimental value, they displayed a little differences due to the different condition: the experimental results in the solid state, but the theoretical results are related to the gas phase

Frontier Molecular Orbital Energy Analysis and Molecular Total Energies

The frontier orbital energy are calculated using DFT method and the results are listed in Table-2.

Table-2: Total energy and frontier orbital energy.

Energy	5a	5b
E_{total}/Hartree [b]	-1592.66256280	-1657.66918806
E_{HOMO}/Hartree	−0.25390	0.01658
E_{LUMO}/Hartree	−0.09262	-0.00728
ΔE [a]/Hartree	0.16128	0.02386

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

According to the FMO theory, LUMO can accept electrons, while HOMO has a priority to provide electrons. Thus, in order to study the structure-active relationship, LUMO and HOMO can give transport information. From the Fig. 3, the geometry of compound 5a and 5b was optimized using B3LYP/6-31G method. The HOMO of compound 5a is mainly located on all the molecule except CN group, while LUMO is only located on the pyridine ring, 1,3,4-thidiazole ring and SCH_2 group. The same phenomenon was found in the compound 5b. The facts are that the electron transitions orient are from the phenyl ring to 1,3,4-thiadiazole ring via SCH_2 bridge with the energy gap is 0.16128 and 0.02386 Hartree respectively.

Mulliken Atomic Charges and ESP

The mulliken atomic charges are listed in Table-3. From Fig. 4, the most negative atoms are focused on the nitrogen atoms (pyridine, thiadiazole and CN group), which can accept electrons firstly. Therefore, the antifungal activity was given, which maybe the amino-acid residue of the fungi interact with nitrogen atoms of the pyridine ring, 1,3,4-thiadiazole ring or CN group.

Table-3: Mulliken atomic charges except for atoms H (e).

5a	DFT	5b	DFT
S1	0.485782	S1	0.428403
S2	0.369834	S2	0.551339
N1	-0.35409	N1	-0.334119
N2	-0.234937	N2	-0.220579
N3	-0.22746	N3	-0.215220
N4	-0.236628	C1	0.063578
C1	0.015095	C2	0.137286
C2	0.14633	C3	0.142941
C3	0.147825	C4	-0.024627
C4	0.085065	C5	0.174235
C5	0.11367	C6	-0.265091
C6	-0.186543	C7	-0.406971
C7	-0.344065	C8	-0.143604
C8	-0.14134	C9	0.090289
C9	0.116294	C10	0.001974
C10	0.051057	C11	-0.072955
C11	0.095641	C12	0.196399
C12	0.080328	C13	-0.078639
C13	0.007178	C14	-0.007513
C14	0.060342	C15	-0.105102
		C16	0.028692
		C17	0.027454
		C18	0.031830

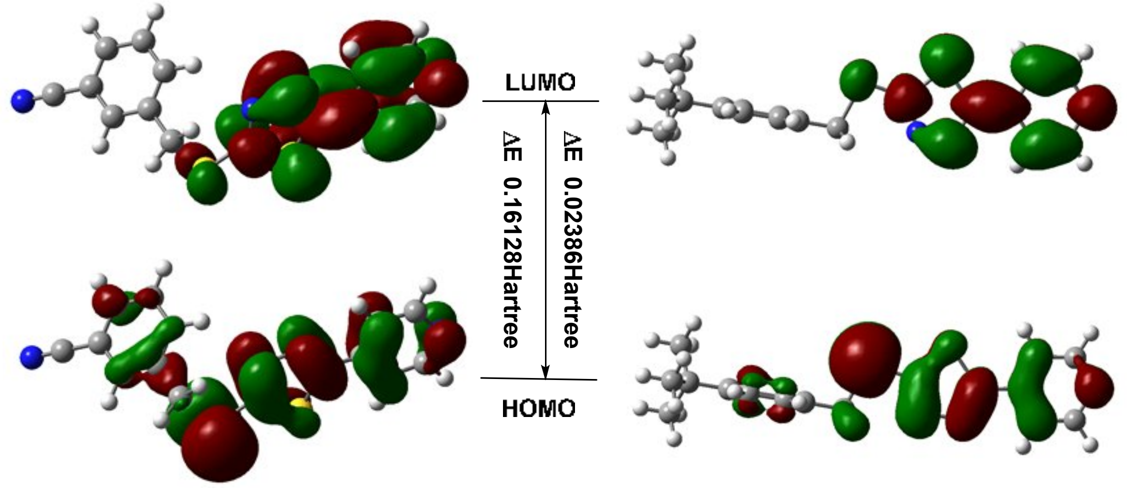
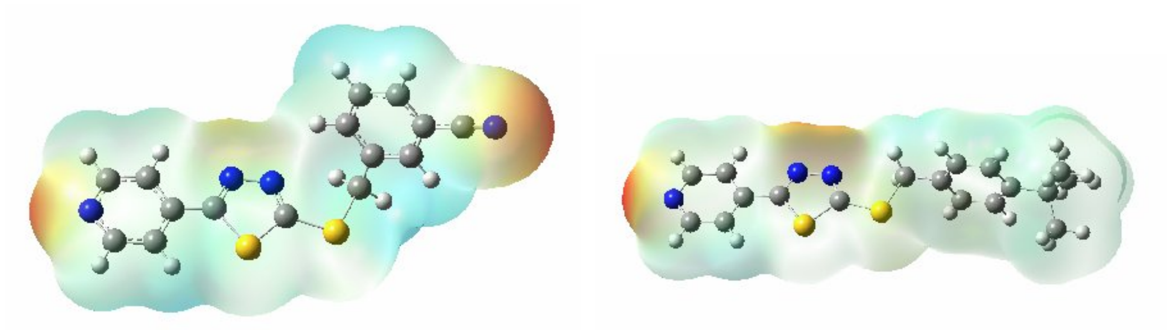


Fig. 3: The HOMO, LUMO and energy gap of compound **5a** and **5b**.



5a **5b**

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

Conclusions

In summary, two novel crystal structures, (3-(((5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl)thio)methyl)benzonitrile and 2-((4-(tert-butyl)benzyl)thio)-5-(pyridin-4-yl)-1,3,4-thiadiazole) were designed and synthesized. The chemical structures was determined by different spectroscopies (NMR, MS, X-RAY) as well as elemental analysis. The X-ray analysis showed that the intermolecular π–π stacking exist in the crystal. The fungicidal activity showed that it displayed moderate activity. Also the calculation was studied by using the DFT method.

Acknowledgements

This work was supported financially by Zhejiang Provincial Science Foundation of China (No. LY16C140007).

References

1. Z.W. Zhai, Y.X. Shi, M.Y. Yang, W. Zhao, Z.H. Sun, J.Q. Weng, C.X. Tan, X.H. Liu, B.J. Li, Y.G. Zhang, Microwave Assisted Synthesis and Antifungal Activity of Some Novel Thioethers Containing 1,2,4-triazolo[4,3-a]pyridine Moiety. *Lett. Drug Des. Discov.* **13**, 521(2016).
2. X.H. Liu, C.X. Tan, J.Q. Weng, Synthesis, dimeric crystal, and fungicidal activity of 1-(4-methylphenyl)-2-(5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone. *Phosphorus Sulfur Silicon Relat. Elem.* **186**, 558(2011).
3. X.H. Liu, W. Zhao, Z.H. Shen, J.H. Xing, J. Yuan, T.M. Xu, W.L. Peng, Synthesis,

Nematocidal Activity and SAR Study of Novel Difluoromethylpyrazole Carboxamide Derivatives Containing Flexible Alkyl Chain Moieties. *Eur. J. Med. Chem.* **125**, 881 (2017).

4. X.H. Liu, Q. Wang, Z.H. Sun, D.E. Wedge, J.J. Becnel, A.S. Estep, C.X. Tan, J.Q. Weng, Synthesis and Insecticidal Activity of Novel Pyrimidine Derivatives Containing Urea pharmacophore against Aedes aegypti. *Pest Manag. Sci.* **73**, 953(2017).
5. X. H. Liu, J. Q. Weng, B. L. Wang and Z. M. Li, Microwave-Assisted Synthesis of Novel Fluorinated 1,2,4-Triazole Derivatives, and Study of their Biological Activity, *Res. Chem. Intermed.*, **40**, 2605 (2014).
6. S. L. Yan, M. Y. Yang, Z. H. Sun, L. J. Min, C. X. Tan, J. Q. Weng, H. K. Wu and X. H. Liu, Synthesis and Antifungal Activity of 1,2,3-thiadiazole Derivatives Containing 1,3,4-thiadiazole Moiety, *Lett. Drug Des. Discov.,* **11,** 940 (2014).
7. Z. H. Sun, Z. W. Zhai, M. Y. Yang, X. H. Liu, C. X. Tan and J. Q. Weng, Microwave Assistant Synthesis and Dimeric Crystal Structure of 2-(((6-Chloropyridin-3-yl)methyl)thio)-5-(pyridin-4-yl)- 1,3,4-thiadiazole, *Chin. J. Struct. Chem.,* **36**, 607 (2014).
8. Z. W. Zhai, M. Y. Yang, Z. H. Sun, X. H. Liu, J. Q. Weng and C. X. Tan, Facile and Efficient Synthesis of Novel 1,2,3-Thiadiazole Derivatives Using Microwave Irradiation, *J. Chem. Res.,* **39**, 311 (2015).
9. N. Rezki, A.M. Al-Yahyawi, S.K. Bardaweel, F.F. Al-Blewi, M.R. Aouad, Synthesis of Novel 2,5-Disubstituted-1,3,4-thiadiazoles Clubbed 1,2,4-Triazole, 1,3,4-Thiadiazole, 1,3,4-Oxadiazole and/or Schiff Base as Potential Antimicrobial and Antiproliferative Agents. *Molecules*, **20**, 16048(2015).
10. N. Polkam, P. Rayam, J.S. Anireddy, S. Yennam, H.S. Anantaraju, S. Dharmarajan, Y. Perumal, S.S. Kotapalli, R. Ummanni, S. Balasubramanian, Synthesis, in vitro anticancer and antimycobacterial evaluation of new 5-(2,5-dimethoxyphenyl)-1,3,4-thiadiazole-2-amino derivatives. *Bioorg. Med. Chem. Lett.* **25**, 1398(2015).
11. J. Ramprasad, N. Nayak, U. Dalimba, P. Yogeeswari, D. Sriram, One-pot synthesis of new triazole—Imidazo[2,1-b][1,3,4]thiadiazole hybrids via click chemistry and evaluation of their antitubercular activity. *Bioorg. Med. Chem. Lett.* **25**, 4169 (2015).
12. P. Li, L. Shi, M.N. Gao, X. Yang, W. Xue, L.H. Jin, D.Y. Hu, B.A. Song, Antibacterial activities against rice bacterial leaf blight and tomato bacterial wilt of 2-mercapto-5-substituted-1,3,4-oxadiazole/thiadiazole derivatives. *Bioorg. Med. Chem. Lett.* **25**, 481 (2015).
13. S.G. Alegaon, M.B. Hirpara, K.R. Alagawadi, K.K. Hullatti, K. Kashniyal, Synthesis of novel pyrazole–thiadiazole hybrid as potential potent and selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.* **24**, 5324(2014).
14. X. H. Liu, X. Y. Xu, C. X. Tan, J. Q. Weng, J. H. Xin and J. Chen, Synthesis, Crystal Structure, Herbicidal Activities and 3D-QSAR Study of Some Novel 1,2,4-triazolo[4,3-*a*]pyridine derivatives, *Pest Manag. Sci.,* **71**, 292 (2015).
15. X. H. Liu, Z. W. Zhai, X. Y. Xu, M. Y. Yang, Z. H. Sun, J. Q. Weng, C. X. Tan and J. Chen, Facile and Efficient Synthesis and Herbicidal Activity Determination of Novel 1,2,4-triazolo[4,3-*a*]pyridin-3(2H)-One Derivatives via Microwave Irradiation. *Bioorg. Med. Chem. Lett.* **25**, 5524 (2015).
16. M. Y. Yang, Z. W. Zhai, Z. H. Sun, S. J. Yu, X. H. Liu, J. Q. Weng, C. X. Tan and W. G. Zhao, A Facile One Pot Synthesis of Novel 1,2,4-triazolo[4,3-*a*]pyridine Derivatives Containing the Trifluoromethyl Moiety via Microwave Irradiation. *J. Chem. Res.* **39**, 521 (2015).
17. X. H. Liu, C. X. Tan and J. Q. Weng, Phase Transfer-Catalyzed, One-Pot Synthesis of Some Novel N-Pyrimidinyl-N'-Nicotinyl Thiourea Derivatives, *Phosphorus Sulfur Silicon Relat. Elem.*, **186**, 552 (2011).
18. H.H.A.M. Hassan, E.M.E. Mansour, A.M.S. Abou Zeid, E.R. El-Helow, A.F. Elhusseiny, R. Soliman, Synthesis and biological evaluation of new nanosized aromatic polyamides containing amido- and sulfonamidopyrimidines pendant structures. *Chem. Cent. J.* **9**, 44(2015).
19. W. Zhao, Z.H. Shen, T.M. Xu, W.L. Peng, X.H. Liu, Synthesis, nematocidal activity and docking study of novel chiral 1-(3-chloropyridin-2-yl)-3-(difluoromethyl)-1H-pyrazole-4- carboxamide derivatives. *J. Heterocycl. Chem.* **54**, 1751(2017).
20. W. Zhao, Z.H. Shen, T.M. Xu, W.L. Peng, X.H. Liu, Synthesis and nematocidal activity of novel pyrazole carboxamide derivatives against Meloidogyne incognita. *Lett. Drug Des. Discov.* **14**, 323(2017).

21. L. J. Zhang, M. Y. Yang, B. Z. Hu, Z. H. Sun, X. H. Liu, J. Q. Weng and C. X. Tan, Microwave-Assisted Synthesis of Novel 8-chloro-[1,2,4]triazolo[4,3-*a*]pyridine Derivatives. *Turk. J. Chem.,* **39**, 1349 (2015).
22. M. Y. Yang, W. Zhao, X. H. Liu, C. X. Tan and J.Q. Weng, Synthesis, Crystal Structure and Antifungal Activity of 4-(5-((2,4-Dichlorobenzyl)thio)-4-phenyl-4H-1,2,4-triazol-3-yl)pyridine, *Chin. J. Struct. Chem.,* **34**, 203(2015).
23. X.H. Liu, W. Zhao, Z.H. Shen, J.H. Xing, J. Yuan, G. Yang, T.M. Xu, W.L. Peng, Synthesis, nematocidal activity and docking study of novel chiral 1-(3-chloropyridin-2-yl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide derivatives. *Bioorg. Med. Chem. Lett.* **26**, 3626 (2016)
24. L. J. Zhang, M. Y. Yang, Z. H. Sun, C. X. Tan, J. Q. Weng, H. K. Wu and X. H. Liu, Synthesis and Antifungal Activity of 1,3,4-Thiadiazole Derivatives Containing Pyridine Group, *Lett. Drug Des. Discov.,* **11,** 1107 (2014).
25. G.M. Sheldrick, *SHELXS97 and SHELXL97*, University of Göttingen, Germany (1997)
26. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, et al. Gaussian 03, revision C. 01; Gaussian, Inc.: Wallingford, CT, USA(2004).
27. Z.H. Shen, Y.X. Shi, M.Y. Yang, Z.H. Sun, J.Q. Weng, C.X. Tan, X.H. Liu, B.J. Li, W.G. Zhao Synthesis, Crystal Structure, DFT Studies and Biological Activity of a Novel Schiff Base Containing Triazolo[4,3-a]pyridine Moiety. *Chin. J. Struct. Chem.*, **35**, 457(2016)
28. Z.W. Zhai, Y.X. Shi, M.Y. Yang, Z.H. Sun, J.Q. Weng, C.X. Tan, X.H. Liu, B.J. Li, Y.G. Zhang, Synthesis, Crystal Structure, DFT Studies and Antifungal Activity of 5-(4-Cyclopropyl-5-((3-fluorobenzyl)sulfonyl)-4H-1,2,4-triazol-3-yl)-4-methyl-1,2,3-thiadiazole. *Chin. J. Struct. Chem.*, **35**, 25(2016).
29. X. H. Liu, C. X. Tan and J. Q. Weng, Synthesis, Dimeric Crystal Structure and Fungicidal Activity of 1-(4-methylphenyl)-2-(5-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone. *Phosphorus Sulfur Silicon Relat. Elem.*, **186**, 558 (2011).
30. Z.H. Shen, Y.X. Shi, M.Y. Yang, Z.H. Sun, J.Q. Weng, C.X. Tan, X.H. Liu, B.J. Li, W.G. Zhao Synthesis, Crystal Structure, DFT Studies and Biological Activity of a Novel Schiff Base Containing Triazolo[4,3-a]pyridine Moiety. *Chin. J. Struct. Chem.*, **35**, 457 (2016)