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Synthesis, Crystal Structure, DFT Study and Antifungal Activity of 4-(5-((4-Bromobenzyl) thio)-4-Phenyl-4*H*-1,2,4-Triazol-3-yl)pyridine

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Abstract: The title compound 4-(5-((4-bromobenzyl)thio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)pyridine ($C_{20}H_{15}BrN_4S$) was synthesized, and its structure was confirmed by ^{1}H NMR, MS and elemental analyses and single-crystal X-ray structure determination. It crystallizes in the triclinic space group *P-1* with a = 7.717(3), b = 9.210(3), c = 13.370(5) Å, α = 80.347(13), β = 77.471(13), γ = 89.899(16)°, V = 913.9(6) Å^3, Z = 2 and R = 0.0260 for 3145 observed reflections with $I > 2\sigma(I)$. A Density functional theory (DFT) (B3LYP/6-31G) calculation of the title molecule was carried out. The full geometry optimization was carried out using a 6-31G basis set, and the frontier orbital energy. Atomic net charges are discussed. Calculated bond lengths and bond angles were found to differ from experimental values, and the compound exhibits moderate antifungal activity.

Keywords: 1,2,4-triazole; pyridine; synthesis; crystal structure; theoretical calculation; antifungal activities

1. Introduction

In recent years, 1,2,4-triazole compounds have represented an important class of nitro-linked heterocyclic compounds, and they are often used in the medicinal or agricultural areas [1–3]. The 1,2,4-triazoles are considered an important nucleus that is associated with numerous biological activities, such as herbicidal [4–6], antifungal [7–9], antiviral [10], GHS-R1a ghrelin receptor [11], antimicrobial [12], anticancer [13], anticonvulsant [14], and antitubercular activities [15]. In addition, Diniconazole, Triadimefon, Triadimenol, Flusilazole, Fluconazole, Itraconazole, which have a 1,2,4-triazole moiety, appear to be very effective. Besides, pyridines display outstanding activities, such as fungicidal [16], herbicidal [17], anticancer [18], antiviral [19], antimicrobial [20], and anti-inflammatory activity [21].

In view of these facts, and also as part of our work [22–26] on the synthesis of bioactive lead compounds for drug discovery, the title compound was designed by introducing pyridine pharmacophore into the 1,2,4-triazole scaffold. This new 1,2,4-triazole derivative characterized by ^{1}H NMR, MS, elemental analysis and single-crystal X-ray structure analysis as well as its antifungal activity has been tested.

2. Results and Discussion

2.1. Crystal Structure

The crystal crystallizes in the triclinic space group *P-1*. The molecular structure is shown in Figure 1, and the packing diagram is in Figure 2. The selected bond lengths and torsion angles are listed in Table 1. CCDC-1438378 contains the supplementary crystallographic data for this crystal. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

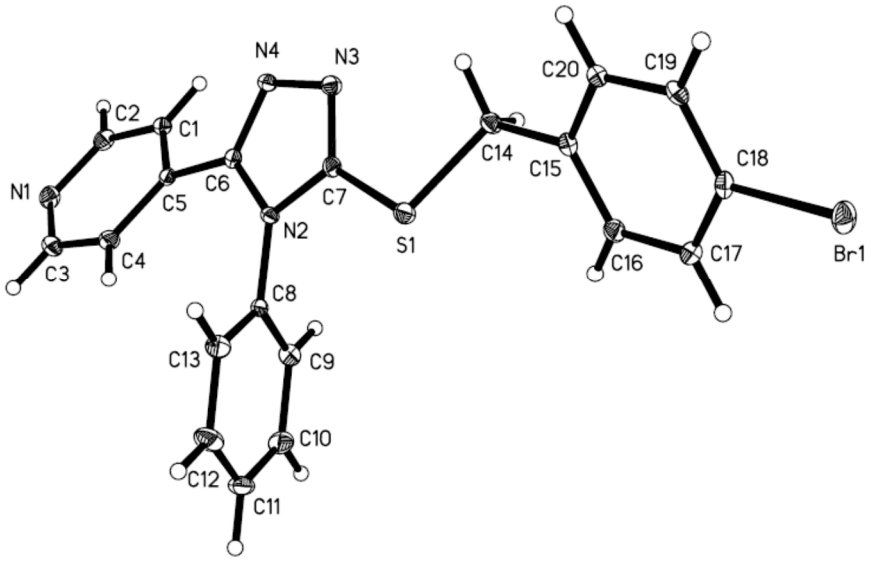


Figure 1. View of the title compound, with displacement ellipsoids drawn at the 30% probability level.

Table 1. Selected bond lengths (Å), angles (°) and theoretical calculations for the title compound.

Bond	X-Ray	DFT	Angle	X-Ray	DFT
Br1–C18	1.9010(19)	1.946	C7–S1–C14	98.36(8)	97.256
S1–C7	1.739(2)	1.808	C3–N1–C2	115.73(17)	117.152
S1–C14	1.8273(18)	1.938	C7–N2–C6	104.50(14)	104.663
N1–C3	1.329(2)	1.350	C7–N2–C8	125.40(15)	125.446
N1–C2	1.343(2)	1.355	C6–N2–C8	129.53(16)	129.696
N2–C7	1.369(2)	1.388	C7–N3–N4	106.70(14)	107.011
N2–C6	1.375(2)	1.404	C6–N4–N3	107.78(14)	108.056
N2–C8	1.445(2)	1.440	C2–C1–C5	119.39(17)	119.274
N3–C7	1.315(2)	1.327	N3–C7–S1	126.94(14)	125.812
N3–N4	1.391(2)	1.408	N2–C7–S1	122.17(13)	123.328
N4–C6	1.311(2)	1.333	N1–C2–C1	124.02(18)	123.374
C1–C2	1.379(2)	1.393	N1–C3–C4	124.92(18)	123.604
C1–C5	1.391(2)	1.410	N4–C6–N2	110.13(15)	109.415
C5–C6	1.473(2)	1.464	C3–C4–C5	118.49(18)	119.022
C8–C9	1.370(3)	1.401	N2–C6–C5	127.01(16)	127.815
C15–C20	1.383(2)	1.406	S1–C14–C15	108.42(12)	108.905

Generally, the average bond lengths and bond angles of ring systems (phenyl, pyridine and triazole) are in normal ranges [27–29]. The C6=N4 bond (1.311(2)Å) in 1,2,4-triazole ring is longer than the general C=N double-bond (imine or Schiff Base) length of 1.27 Å. The bond angle of C7–S1–C14 is 98.36(7)°. The torsion angle of the thioether group C7–S1–C14–C15 is 174.13(10)°. From Table 1, calculated bond lengths and bond angles were found to differ from experimental values. For example,

the bond S1–C14 is 1.938 Å in our calculation result, but it is shorter in the crystal with the bond length of 1.8273(18) Å.

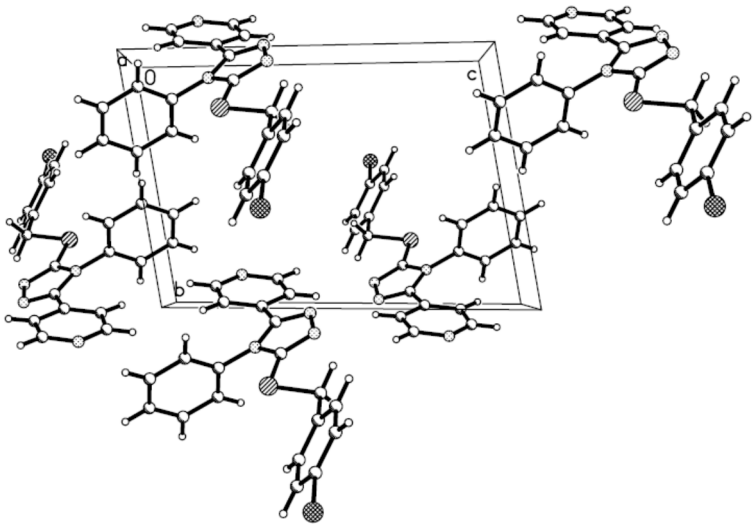


Figure 2. A view of pack title compound.

As shown in Figure 1, each of the four rings is planar. The interplanar angles between the triazole ring on the one hand and the pyridine, phenyl (C8–C13) and phenyl (C15–C20) rings on the other hand are 23.9°, 72.9° and 37.5°, respectively. Meanwhile, the mean plane of the pyridine ring forms angles of 72.4° and 60.6°, respectively, with the phenyl rings (C8–C13) and (C15–C20). The planes of the two phenyl rings form an angle of 68.7° with one another.

An interesting feature is the intramolecular edge-to-face π–π stacking, which exists between the CH and the two phenyl rings (C8–C13 and C15–C20) (Figure 2); the distances between the CH and the centroids of the phenyl rings are 3.439 and 2.833 Å, and the angles of CH and the centroids of phenyl ring and pyridine ring are 88.05° and 87.42°, respectively. Between the CH of the phenyl ring and pyridine ring, the intramolecular edge-to-face π–π stacking also exists, with the distance between the CH and the centroid of the pyridine ring is 2.666 Å, and the angle of CH and the centroid of the pyridine ring is 85.38°, respectively. In addition, the intermolecular face-to-face π–π stackings exist between two phenyl rings: the centroid separation of them is 3.8744(18) Å (C15–C20), and the dihedral angle between the two π planes is 0.00°. These interactions are estimated to play a role in stabilizing the crystal structure.

2.2. Frontier Orbital Energy Analysis and Molecular Total Energies

Molecular total energy and frontier orbital energy levels are listed in Table 2.

Table 2. Total energy and frontier orbital energy.

Energy	DFT
E_{total}/Hartree [b]	−3959.60345337
E_{HOMO}/Hartree	−0.23217
E_{LUMO}/Hartree	−0.05718
ΔE [a]/Hartree	0.17499

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

The energy gap between Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) was calculated by Becke's nonlocal three parameter exchange and

correlation functional with Lee-Yang-Parr correlation functional (B3LYP). According to the frontier molecular orbital theory, HOMO and LUMO are the most important factors that affect the bioactivity. HOMO has a priority to provide electrons, while LUMO can accept electrons firstly. Thus, study on the frontier orbital energy can provide useful information about the biological mechanism. From the Figure 3, the geometry of the title compound was optimized using the DFT method. The LUMO of the title compound is mainly located on the pyridine ring, 1,2,4-triazole ring, phenyl ring and SCH_2 group, while the HOMO of the title compound is located on the pyridine ring, 1,2,4-triazole ring and SCH_2 group. The fact is that the electron transitions from the pyridine ring, 1,2,4-triazole ring and SCH_2 group to the phenyl ring, while the energy gap between the HOMO and LUMO is 0.17499 Hartree.

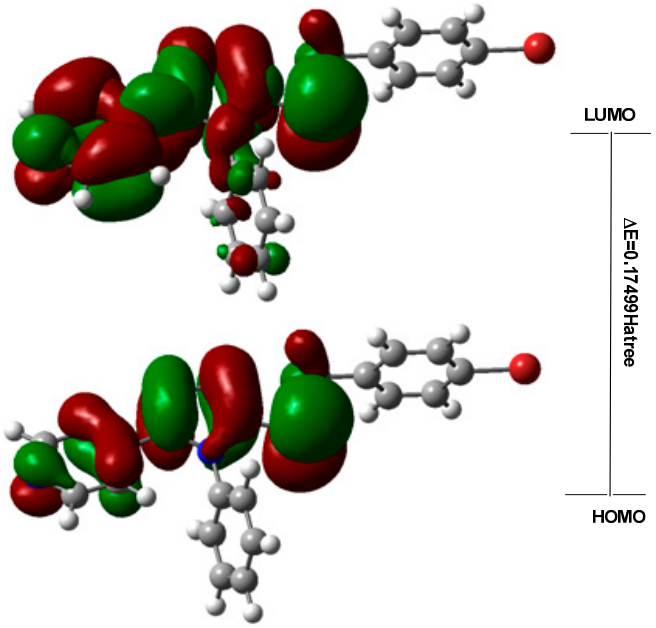


Figure 3. Frontier molecular orbitals of **5**.

2.3. Mulliken Atomic Charges and Electrostatic Potential (ESP)

Table 3 exhibits the calculated mulliken atomic charges except for atoms H. Taking DFT, for example, again (Figure 4), all the nitrogen atoms (N1, N3, N4) are the most negatively charged ones, which can interact with the positively charged part of the receptor easily. Therefore, we supposed this compound can combine the amino-acid residue on its surface by the interaction of the pyridine ring or 1,2,4-triazole ring, which may be responsible for the bioactivity.

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

Atom	DFT	Atom	DFT
Br	0.153554	C8	0.193822
S	0.414796	C9	0.087561
N1	−0.34484	C10	0.001415
N2	−0.74971	C11	0.045526
N3	−0.2961	C12	0.002975
N4	−0.29831	C13	0.081998
C1	0.039917	C14	−0.13113
C2	0.137539	C15	0.095849
C3	0.130136	C16	0.016004
C4	0.018614	C17	0.067704
C5	0.144262	C18	−0.31752
C6	0.331575	C19	0.068198
C7	0.112535	C20	−0.00637

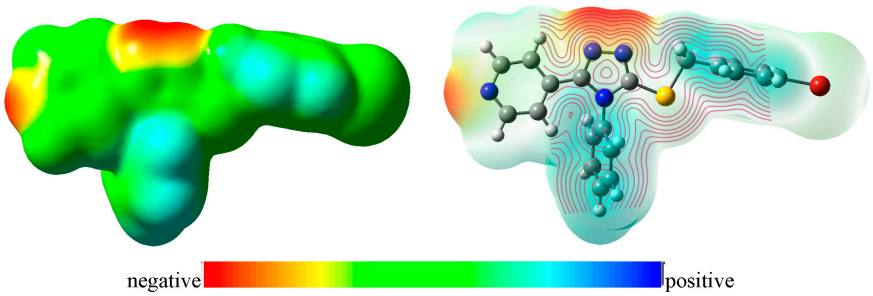


Figure 4. Electrostatic potential mapping on the electron density (isovalue = 0.04).

2.4. Evaluation of the Bioactivity

The *in vivo* fungicidal activities of the title compound against *Stemphylium lycopersici* (Enjoji) Yamamoto, *Fusarium oxysporum.* sp. cucumebrium and *Botrytis cinerea* were evaluated; Zhongshengmycin, Thiophanate-Methyl and Cyprodinil were used as controls. The primary bioassay showed the title compound exhibits weak inhibiting activity towards *Stemphylium lycopersici* (Enjoji) Yamamoto, *Fusarium oxysporum.* sp. cucumebrium and *Botrytis cinerea*. Its inhibition rates to *Stemphylium lycopersici* (Enjoji) Yamamoto, *Fusarium oxysporum.* sp. cucumebrium and *Botrytis cinerea* reached 42.86%, 64.44%, 6.67% at 500 μg/mL, respectively, and it is lower than that of the controls (Zhongshengmycin, 59.58%; Thiophanate-Methyl, 81.69%; Cyprodinil, 45.56%).

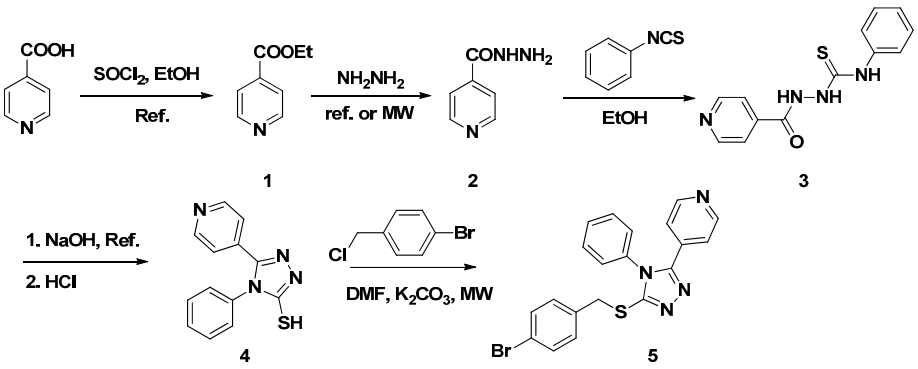
3. Experimental Section

3.1. Instruments

Melting points were determined using an X-4 apparatus and uncorrected. The ^{1}H NMR spectra were measured on a Bruker AV-400 instrument (Fallanden, Switzerland) using TMS as an internal standard and $CDCl_3$ as the solvent. Elemental analyses were performed on a Vario EL elemental analyzer (Hanau, Germany). Crystallographic data of the compound were collected on a rigaku saturn diffractometer (Tokyo, Japan). All the reagents are of analytical grade or freshly prepared before use.

3.2. General Procedure

The synthetic route of title compound was outlined in Scheme 1. The intermediate **1**, **2** was synthesized according to the reference [30,31]. A mixture of isonicotinyl hydrazine (1.37 g, 10 mmol) with isothiocyanatobenzene (1.35 g, 10 mmol) was refluxed for 5 h in ethanol. After cooling down to room temperature, the products were obtained and recrystallized from methanol to give **3**, yield 95%. A mixture of compound **3** (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 **4**, yield 88%. A CEM designed 10 mL pressure-rated vial was charged with DMF (5 mL), **4** (0.25 g, 1 mmol), 4-bromo-1-(chloromethyl)benzene (1.1 mmol), and NaOH (0.05 g, 1.2 mmol). The mixture was irradiated in a CEM Discover Focused Synthesizer (Matthews, MO, USA) (150 W, 90 °C, 200 psi, 15 min). The mixture was cooled to room temperature by passing compressed air through the microwave cavity for 2 min. It was poured into cold ice (40 mL) and the formed precipitate was filtered. The crude solid was recrystallized from EtOH to give the title compound. 4-(5-((4-bromobenzyl)thio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)pyridine: white crystal, yield 90%, m.p. 161–163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 4.48 (s, 2H, SCH_2), 7.15 (d, J = 7.2 Hz, 2H, Py), 7.28–7.32 (m, 4H, ArH), 7.42 (d, J = 8.3 Hz, 2H, Ar-H), 7.51–7.60 (m, 3H, ArH). 8.60 (bs, 2H, Py). MS (ESI), m/z: 424 $(M + 1)^+$. Elemental anal. (%), calculated: C, 56.74; H, 3.57; N, 13.23; found: C, 56.87; H, 3.67; N,13.43.



Scheme 1. The synthetic route of title compound.

3.3. Structure Determination

The cube-shaped single crystal of the title compound was obtained by recrystallization from EtOH. The crystal size is 0.20 mm × 0.18 mm × 0.14 mm. A total of 9617 reflections were collected, 4313 of which were independent (R_{int} = 0.031) and 3145 were observed with $I > 2\sigma(I)$. The calculations were performed with SHELXS-97 program [32] and the empirical absorption corrections were applied to all intensity data. The non-hydrogen atoms were refined anisotropically. The positions of H atoms were refined using riding models. A summary of the key crystallgraphic information was given in Table 4.

Table 4. Crystal data of the title compound **5**.

CCDC No.	1438378
Empirical Formula	$C_{20}H_{15}BrN_4S$
Formula weight	423.33
T/K	113(2)
λ/nm	0.071073
Crystal system, space group	Triclinic, *P-1*
Unit cell dimensions	a = 7.717(3) Å, α = 80.347(13)° b = 9.210(3) Å, β = 77.471(13)° c = 13.370(5) Å, γ = 89.899(16)°
V/nm^3	913.9(6) Å^3
Z	2
Calculated density/(g·cm^{-3})	1.538
Absorption coefficient/mm^{-1}	2.374
Reflections collected/unique	9617/4313 ($R_{(int)}$ = 0.0306)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4313/0/235
Goodness-of-fit on F^2	1.059
Final R indices ($I > 2\ \sigma$(I))	R_1 = 0.0263, wR_2 = 0.0567
Largest diff. peak and hole	0.713 and −0.281 e/Å^3

3.4. Therotical Calculations

According to the above crystal structure, a crystal unit was selected as the initial structure, while DFT-B3LYP/6-31G methods in Gaussian 03 package [33] were used to optimize the structure of the

title compound. Vibration analysis showed that the optimized structures were in accordance with the minimum points on the potential energy surfaces, which means no virtual frequencies, proving that the obtained optimized structures were stable. All the convergent precisions were the system default values, and all the calculations were carried out on a DELL computer.

3.5. Antifungal Activity

Antifungal activities of compound **5** against *Stemphylium lycopersici* (Enjoji) Yamamoto, *Fusarium oxysporum.* sp. cucumebrium and *Botrytis cinerea* were evaluated according to references [34,35].

4. Conclusions

In summary, a new crystal structure, 4-(5-((4-bromobenzyl)thio)-4-phenyl-4H-1,2,4-triazol-3-yl)pyridine, has been prepared by multi-step reaction and characterized by ^{1}H NMR, MS and elemental analyses and single-crystal X-ray structure determination. The results show that the crystal structure exhibits intermolecular π–π stacking. The frontier orbital energy analysis, mulliken atomic charges and electrostatic potential were also studied by using the DFT method. The antifungal bioassay showed that it possessed moderate activity.

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Author Contributions: Jin-Xia Mu, Ming-Yan Yang and Zhao-Hui Sun carried out experimental work, Zhi-Wen Zhai revised and write the paper, Hong-Ke Wu discussed the experimental data. Xing-Hai Liu designed the material and supervised the project.

Conflicts of Interest: The authors declare no conflict of interest.

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