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Synthesis, Crystal Structure and Antibacterial Activity of (E)-Methyl 2-(2-(((4-((E)-(4-methoxybenzylidene)amino)-5-phenyl-4H-1,2,4-triazol-3-yl)thio)methyl)phenyl)-2-(methoxyimino)acetate

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(E)-Methyl 2-(2-(((4-((E)-(4-methoxybenzylidene)amino)-5-phenyl-4H-1,2,4-triazol -3-yl)thio)methyl)phenyl)-2-(methoxyimino)acetate has been synthesized and its structure was characterized by IR, ^{1}H NMR, H RMS and single crystal X-ray diffraction. The preliminary biological activity assay results showed that the compound exhibited moderate antibacterial activity against *Blumeria graminis*.

Keywords: Crystal structure, Strobilurin, Antibacterial activity.

INTRODUCTION

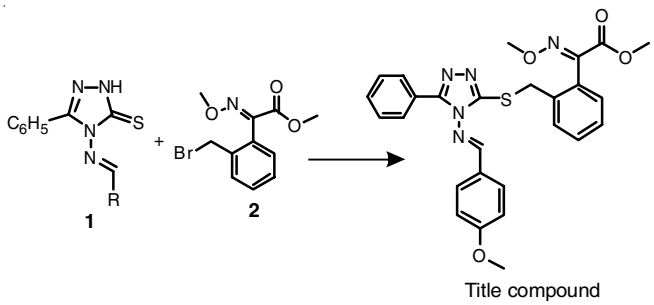
The strobilurins are known as one of the most important classes of agricultural fungicides, with a broad spectrum, long duration, high antifungal activity and low toxicity toward mammalian cells and environmentally benign characteristics [1-4]. Their primary action mechanism is the inhibition of mitochondrial respiration. So far, thousands of analogues have been synthesized [5,6].

Using the intermediate derivatization method based on the active substructure combination and bioisosteric replacement, a series of novel strobilurin derivatives containing 1,2,4-triazolo moieties and strobilurin pharmacophore were designed and synthesized with the aim of obtaining more active candidates. (E)-Methyl 2-(2-(((4-((E)-(4-methoxybenzylidene)-amino)-5-phenyl-4H-1,2,4-triazol-3-yl)thio)methyl)phenyl)-2-(methoxyimino)acetate has been synthesized by the condensation of 4-methylbenzohydrazide and 2-bromobenzaldehyde and its crystal structure was determined by X-ray crystallography. Furthermore, preliminary antibacterial activity against *Rhizoctonia solani*, *Botrytis cinereapers*, *Fusarium graminearum* and *Blumeria graminis* was tested.

EXPERIMENTAL

All chemicals and reagents were of analytical grade and used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE-600 MHz NMR spectrometer using TMS as internal standard. Molecular weights of monomers were determined by high resolution mass spectroscopy.

Synthesis of the compound: The synthesis procedure is shown in **Scheme-I**. (E)-3-Thiol-4-(4-methoxybenzylidene-amino)-5-phenyl-4H-1,2,4-triazole (**1**) (1.75 mmol) was dissolved in DMF (15 mL) and anhydrous potassium carbonate (0.24 g, 1.75 mmol) was added to the solution. The solution was stirred for 0.5 h and methyl (*E*)-methyl 2-(2-bromomethyl-phenyl)-2-(methoxyimino)acetate (**2**) (0.50 g, 1.75 mmol) was then added. The reaction mixture was heated to 80 °C and monitored by TLC. After 1 h, the mixture was cooled, diluted with water (30 mL) and extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was evaporated and the crude product was purified by silica gel column chromatography using a 1:3 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range 60-90 °C) as



Scheme-I: Synthesis route of the title compound

the eluting solution to obtain title compound. White solid, Yield: 68.6 %, m.p.: 105-106 °C ; IR: (KBr, cm^{-1}): 3100, 2957, 1651, 1604, 1557, 1524, 1490, 1280; ^1H NMR (600 MHz, DMSO-d_6) δ: 3.66 (s, 3H, $COOCH_3$), 3.86 (s, 3H, =N-OCH_3), 3.90 (s, 3H, Ar-OCH_3), 4.28 (s, 2H, CH_2), 7.13 (d, *J* =7.3 Hz, 2H, ArH), 7.16 (d, *J* = 7.3 Hz, 1H, ArH), 7.31-7.50 (m, 5H, ArH), 7.54 (d, *J* = 7.3 Hz, 1H, ArH), 7.83 (d, *J* = 8.1 Hz, 4H, ArH), 8.63 (s, 1H, CH=N); H RMS calcd. for $C_{27}H_{26}N_5O_4S$ $[M+H]^+$ 516.17000, found 516.16997.

X-ray crystal structure determination: A yellow single crystal of the title compound (0.60 mm × 0.50 mm × 0.40 mm) was selected and mounted on the top of a glass fiber. X-ray single-crystal diffraction measurement was carried out at 296 K on a Bruker Smart APEX 1000 CCD area diffractometer equipped with a graphite-monochromatic MoK_α radiation (λ = 0.71073 Å) for data collection. The structure was solved by direct methods with SHELXS-97 program and refined by full-matrix least-squares techniques on F2 with SHELXL-97 program. All non-H atoms were refined anisotropically and allowed to ride on their parent carbon atoms. A full-matrix least-squares refinement gave the final R = 0.0292 and wR = 0.0674 ($w = 1/[\sigma^2(Fo^2) + (0.0256\ P)_2 + 0.3938\ P]$, where $P = (Fo^2 + 2Fc^2)/3$). S = 1.019, $(\Delta/\sigma)_{max} = 0.001$, $(\Delta\rho)_{max} = 0.453$ e Å^{-3}, $(\Delta\rho)_{min} = -0.313$ e Å^{-3}. All calculations were performed using the crystal structure crystallographic software package except for the refinement. All H atoms were placed in the geometrically idealized positions and allowed to ride on their respective parent atoms, with the C-H distance of 0.9500-0.9800 Å and Uiso (H) = 1.2 or 1.5 Ueq (C/O).

Antibacterial activity: Under the condition of laboratory, inhibitive activity of newly prepared compounds were tested by means of mycelium growth rate method and these strobilurin derivatives were screened for antifungal activity against *Rhizoctonia solani*, *Botrytis cinereapers*, *Fusarium graminearum* and *Blumeria graminis* at dosages of 50 μg/mL. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with kresoxim-methyl as standard. The results of preliminary screening are summarized in Table-1.

TABLE-1
ANTIBACTERIAL ACTIVITY OF THE TITLE COMPOUND (INHIBITION RATE, %, 50 μg/mL)

Entry	*Rhizoctonia solani*	*Botrytis cinereapers*	*Fusarium graminearum*	*Blumeria graminis*
Title compound	12.96	14.55	10.95	42.61
Kresoxim-methyl	65.32	81.69	73.36	100

RESULTS AND DISCUSSION

The crystallographic data and experimental details of structural analyses for coordination polymers are summarized in Table-2. The selected bond lengths and bond angles are summarized in Table-3. The molecular structure and packing diagram of title compound are shown in Figs. 1 and 2, respectively.

As shown in Table-3, the bond length of 1.268(2) Å between atoms N(1) and C(9) is nearly the same as that of typical N=C bond in other Schiff bases [7]. Suggesting it to be a double bond exists as an E configuration. Owing to the conjugation effects of 1,2,4-triazole in the molecules, the two benzene rings are not coplanar with a dihedral angle of 26.32°. The torsion angle of N (2)–N (1)–C (9)–C (10) is 176.51 (2)° and the N=C bond of methyl acrylate was also E configuration, the torsion angle of C(25)–C(24)–N(5)–O(4) is 179.75 (2)°. In addition, there are no classic hydrogen bonds found and the molecular and crystal structures are stabilized mainly by the π-π interaction.

TABLE-2
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR THE TITLE COMPOUND

Empirical formula	$C_{27}H_{25}N_5O_4S$
Formula weight	515.58
Temperature	296(2) K
Crystal system	Monoclinic
Space group	P21/c
Cell dimensions, (Å, °)	a = 14.6736(5), α = 90° b = 19.4763(7) A, β = 90.3510(10)° c = 8.9668(3) A, γ = 90°
Volume (Å^3)	2562.55(15)
Z	4
Density (calculated)	1.336 Mg/m^3
Absorption coefficient	0.170 mm^{-1}
F(000)	1080
Index ranges	-20 ≤ h ≤ 20, -27 ≤ k ≤ 26, -12 ≤ l ≤ 9
Reflections collected	16040
Independent reflections	6192 (Rint = 0.0379)
Data/restraints/parameters	6192/0/337
Goodness of fit on F^2	0.750
R [I > 2σ(I)]	R1 = 0.0434, wR2 = 0.0835
R indices (all data)	R1 = 0.1222, wR2 = 0.1002
Largest diff. peak and hole (e Å^{-3})	0.131 and -0.143

TABLE-3
SELECTED BOND LENGTHS (Å) AND BOND ANGLES (°)

C(1)-C(6)	1.394(2)	N(4)-C(8)-N(2)	110.77(15)
C(5) -C(6)	1.364(2)	N(4)-C(8)-S(1)	125.89(13)
C(7) -N(3)	1.317(2)	N(2)-C(8)-S(1)	123.18(13)
C(7) - N(2)	1.376(2)	N(1)-C(9)-C(10)	121.77(17)
C(8) -N(4)	1.306(2)	C(15)-C(10)-C(9)	118.47(16)
C(8) - N(2)	1.362(2)	C(11)-C(10)-C(9)	123.40(15)
C(8) -S(1)	1.7511(2)	C(19)-C(18)-C(17)	120.05(17)
C(9) -N(1)	1.268(2)	C(23)-C(18)-C(17)	122.06(14)
C(9) -C(10)	1.453(2)	C(22)-C(23)-C(24)	117.86(15)
C(10) - C(15)	1.382(2)	C(18)-C(23)-C(24)	121.91(13)
C(10) -C(11)	1.386(2)	N(5)-C(24)-C(23)	127.52(14)
C(17) -C(18)	1.495(2)	N(5)-C(24)-C(25)	116.16(14)
C(17) - S(1)	1.8122(2)	C(23)-C(24)-C(25)	116.31(13)
C(23) -C(24)	1.495(2)	O(3)-C(25)-O(2)	124.56(16)
C(24) - N(5)	1.2826(18)	C(9)-N(1)-N(2)	113.96(15)
C(24) -C(25)	1.499(2)	C(8)-N(2)-C(7)	105.39(13)
N(1) -N(2)	1.4141(18)	C(8)-N(2)-N(1)	129.58(13)
N(3) - N(4)	1.385(2)	C(7)-N(2)-N(1)	124.56(13)
N(5) -O(4)	1.3883(17)	C(7)-N(3)-N(4)	108.53(13)
C(5)-C(6)-C(1)	117.53(17)	C(8)-N(4)-N(3)	106.68(13)
C(5)-C(6)-C(7)	126.05(16)	C(24)-N(5)-O(4)	111.85(12)
C(1)-C(6)-C(7)	116.41(15)	C(13)-O(1)-C(16)	116.77(16)
N(3)-C(7)-N(2)	108.56(15)	C(25)-O(2)-C(26)	116.35(15)
N(3)-C(7)-C(6)	123.56(15)	N(5)-O(4)-C(27)	109.34(13)
N(2)-C(7)-C(6)	127.88(14)	C(8)-S(1)-C(17)	98.07(8)

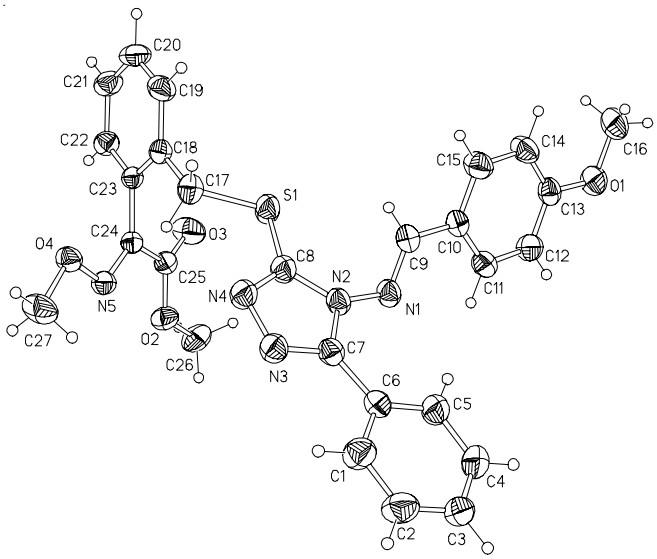


Fig. 1. Molecular structure of the title compound

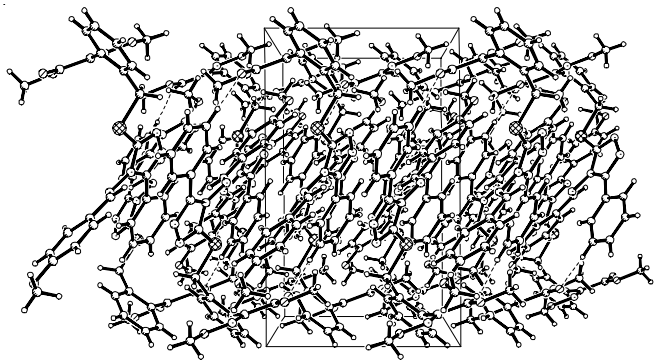


Fig. 2. Packing diagram of the title compound

The antibacterial activity of the title compound was evaluated against *Rhizoctonia solani*, *Botrytis cinereapers*, *Fusarium graminearum* and *Blumeria graminis.* It can be observed that the title compound exhibits a moderate antibacterial activity against *Blumeria graminis*.

Conclusion

In summary, (E)-methyl 2-(2-(((4-((E)-(4-methoxybenzylidene)amino)-5-phenyl-4H-1,2,4-triazol-3-yl)thio)methyl)-phenyl)-2-(methoxyimino)acetate was synthesized using a simple method and possessing a moderate application value, which provides basic data for further research and creating new compounds.

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