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Synthesis, Crystal Structure and Antibacterial Activity of 2-(*p*-Tolyl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole

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The compound 2-(*p*-tolyl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (m.f. $C_{18}H_{18}N_2O_4$) was synthesized and characterized by ^{1}H NMR, ^{13}C NMR, MS and X-ray single crystal diffraction analysis. In the crystal structure, the two phenyl rings and the 1,3,4-oxadiazole ring are nearly coplanar with the dihedral angles 4.55, 1.13 and 3.97°. There is an offset face-to-face π-π stacking interaction between 1,3,4-oxadiazole ring planes. The compound molecules are connected through the offset face-to-face π-π stacking interactions to generate a three-dimensional network. The results of preliminary biological activity assay showed that the title compound exhibited good antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

Keywords: 1,3,4-Oxadiazole, Crystal structure, Synthesis, Antibacterial activity.

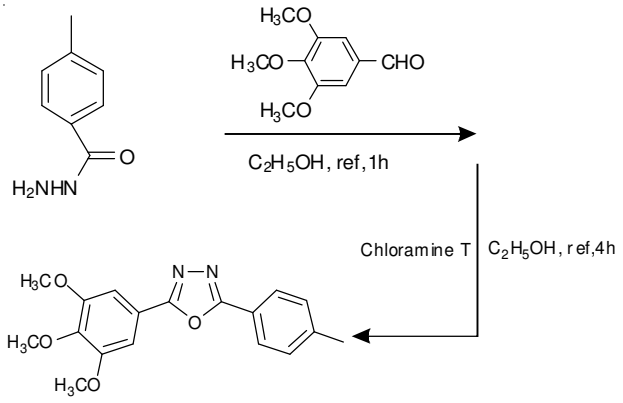
INTRODUCTION

The wide occurrence of the heterocycles in bioactive natural products and pharmaceuticals has made them as important synthetic targets. 1,3,4-Oxadiazoles are a class of heterocyclic compounds which have great importance in medicinal chemistry. During the last few decades, considerable attention has been devoted to the synthesis of 1,3,4-oxadiazole derivatives which have been found to exhibit diverse biological activities such as antibacterial[1,2], antifungal[3,4], antiinflammatory[5], analgesic[6], anticonvulsant[7] and insecticidal activities[8-10]. Moreover, substituted 1,3,4-oxadiazoles also revealed anticancer[11,12] and tyrosinase inhibitory activities[13,14]. In this paper, 2-(*p*-tolyl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole was efficiently synthesized by the condensation of 4-methylbenzohydrazide and 3,4,5-trimethoxy-benzaldehyde in ethanol solution with chloramine-T. Its crystal structure was determined by X-ray single crystal diffraction analysis. Furthermore, preliminary antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* was investigated.

EXPERIMENTAL

All reagents were of analytical grade and used without further purification. Melting point was measured with an OPM100 OptiMelt apparatus and was uncorrected. ^{1}H NMR and ^{13}C NMR spectra were performed on a Bruker AVANCE-400 MHz NMR spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectrum was recorded on a Bruker Esquire HCTplus spectrometer (APCI).

General procedure: The title compound was synthesized according to **Scheme-I**. 4-Methylbenzohydrazide (1.50 g, 0.01 mol) and 3,4,5-trimethoxybenzaldehyde (1.96 g, 0.01 mol) were dissolved in ethanol (50 mL). The mixture was refluxed for 1 h until the starting materials disappeared (monitored by TLC) to give a clear white solution. Chloramine-T (14.08 g, 0.05 mol) was added into the mixture and stirred for 4 h at 76 °C. Excess ethanol was evaporated under reduced pressure, the mixture was washed with water and filtered. Then, the crude product was recrystallized from acetone to give 2.5 g colorless crystals with a yield of 76.7 %. m.p. 192-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.00 (d, *J* = 8.1 Hz, 2H, C_6H_4, 2,6-H), 7.38 -7.25 (m, 4H, C_6H_2, 2,6-H C_6H_4, 3,5-H), 3.97 (s, 6H, OCH_3), 3.93 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3);



Scheme-I: Synthesis route of the title compound

^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.60, 164.20, 153.65, 142.25, 141.13, 129.72, 126.82, 121.05, 119.03, 104.18, 60.96, 56.38, 21.60. APCI MS: *m/z*, 327.3 (M + 1, 100).

Determination of crystal structure: The colorless crystals were dissolved in ethanol. Single crystals suitable for X-ray analysis were obtained by slowly evaporation of the solvent. A colorless block crystal of the title compound with dimensions of 0.44 mm × 0.42 mm × 0.35 mm was selected for data collection which was performed on a Bruker Smart APEX 1000 CCD diffractometer equipped with a graphite-monochromatic MoK_α radiation (λ = 0.71073 Å) by using a ω scan mode at 173(2) K. The structure was solved by direct methods with SHELXS-97 program[15] and refined by full-matrix least-squares techniques on F^2 with SHELXL-97 program[16]. All non-H atoms were refined anisotropically. All H atoms were placed in the geometrically idealized positions and allowed to ride on their respective parent atoms, with C-H distance in the range of 0.9500-0.9800 Å and U_{iso}(H) = 1.2 or 1.5 U_{eq}(C/O). All calculations were performed using the crystal structure crystallographic software package except for the refinement. The detailed crystal data, recording conditions and refinement results are listed in Table-1.

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR THE TITLE COMPOUND

Empirical formula	$C_{18}H_{18}N_2O_4$
Formula weight	326.34
Crystal dimensions (mm^3)	0.44 × 0.42 × 0.35
Temperature (K)	173(2)
Wavelength (Å)	0.71073 Å (MoKa)
Crystal system	Triclinic
Space group	P $\bar{1}$
a(Å)	8.0844(5)
b(Å)	8.1802(5)
c(Å)	12.5772(8)
α(°)	91.0410(10)
β(°)	100.9570(10)
γ(°)	99.138(10)
V($Å^3$)	805.22(9)
Z	2
D_C (g cm^{-3})	1.346
Absorption coefficient (mm^{-1})	0.096
F(000)	344
Theta range for data collection (°)	2.53 to 27.01°
Index ranges	-9 ≤ h ≤ 9, -10 ≤ k ≤ 9, -15 ≤ l ≤ 15
Reflections collected	6215
Independent reflections	3087 [$R_{(int)}$ = 0.0384]
Data/restraints/parameters	3087/0/221
Goodness-of-fit on F^2	1.051
Final *R* indices [I >2 σ (I)]	R_1 = 0.0384, wR_2 = 0.1084
R indices (all data)	R_1 = 0.0498, wR_2 = 0.1174
Largest diff. peak and hole (e. $Å^{-3}$)	0.212 and -0.194

Determination of antibacterial activity: The antibacterial activity of title compound against *S. aureus* and *E. coli* were evaluated by the modified agar diffusion method[17]. The compound was dissolved in DMF. After encapsulation, autoclave sterilization at 121 °C for 20 min, nutrient agar was transferred to petri dish and frozen after cooling. After the test strains were spread on the solid nutrient agar surface, three stainless steel tubes (7.8 mm × 6 mm × 10 mm) were placed on the surface vertically, into which 100 µL compound with certain concentration was injected. The inhibition was labeled as the diameter of transparent bacteriostatic circle after an incubation period of 24 h at 37 °C. Blank tests showed that DMF in preparing the test solutions does not affect the test organisms. All tests were repeated three times and average data were taken as the final result.

RESULTS AND DISCUSSION

The molecular structure of the title compound with atomic numbering is shown in Fig. 1. The structure of the title compound is in a triclinic crystal system with a P $\bar{1}$ space group. The title compound contains two phenyl rings and a 1,3,4-oxadiazole ring. The dihedral angle between the phenyl ring (C(3), C(5)-C(9)) and 1,3,4-oxadiazole ring is 4.55°, between the phenyl ring (C(4), C(10)-C(14)) and 1,3,4-oxadiazole ring is 1.13° and that between the phenyl ring (C(3), C(5)-C(9)) and the phenyl ring (C(4), C(10)-C(14)) is 3.97°. All these dihedral angles are so small that the three rings nearly construct a plane, providing a large conjugated system within the molecule. Selected bond lengths and bond angles are given in Table-2. The results reveal that the bond length of C(1)-N(2) and C(2)-N(1) are 1.2900(19) Å and 1.2882(19) Å, which are between typical C-N single bond (1.47 Å) and C=N double bonds (1.27 Å). The C-C bond lengths on the molecular skeleton are also between typical C-C single bond (1.54 Å) and C=C double bonds (1.34 Å). This indicates that π-electrons in the molecular are delocalized. In this structure, there is an offset face-to-face π-π stacking interaction between 1,3,4-oxadiazole rings with perpendicular distance (3.3468(6) Å) and centroid-centroid distance (5.2629(9) Å). The offset face-to-face π-π stacking interactions link the molecule into a three-dimensional network which further stabilizes the molecular structure.

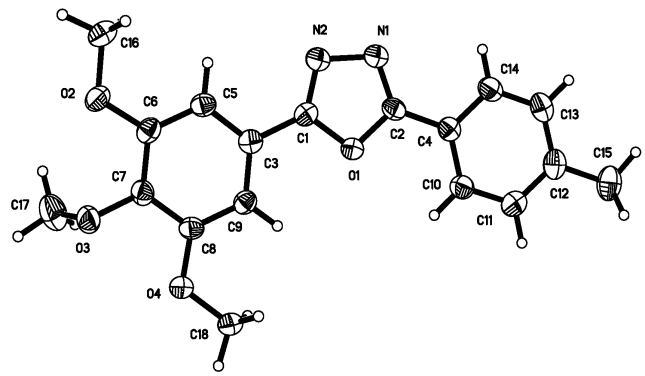


Fig. 1. Molecular structure of the title compound with 50 % probability displacement ellipsoids

The antibacterial activity of the title compound was evaluated against *S. aureus* and *E. coli*. The test results are reported in Table-3. It can be observed that the title compound exhibits antibacterial activity against both test bacterial organisms. At the concentration of 5.0 mg/mL, the title compound exhibits good antibacterial activity (inhibition zone diameter: 20.1 mm) against *S. aureus*. The inhibition effect is strengthened with

TABLE-2
SELECTED BOND LENGTHS (Å) AND BOND ANGLES (°) FOR THE TITLE COMPOUND

Bond	Lengths	Bond	Lengths
C(1)-N(2)	1.2900(19)	C(6)-C(7)	1.4010(2)
C(1)-O(1)	1.3645(17)	C(7)-O(3)	1.3735(17)
C(2)-N(1)	1.2882(19)	C(10)-C(11)	1.3810(2)
C(2)-O(1)	1.3700(16)	C(11)-C(12)	1.3920(2)
C(1)-C(3)	1.4580(2)	C(12)-C(13)	1.3880(2)
C(2)-C(4)	1.4510(2)	C(12)-C(15)	1.5030(2)
C(3)-C(5)	1.3890(2)	C(16)-O(2)	1.4288(18)
C(4)-C(10)	1.3910(2)	C(17)-O(3)	1.4230(2)
C(5)-C(6)	1.3870(2)	N(1)-N(2)	1.4066(18)
Bond	Angles	Bond	Angles
N(1)-C(2)-O(1)	112.39(12)	C(5)-C(6)-C(7)	120.36(13)
N(1)-C(2)-C(4)	128.26(13)	O(3)-C(7)-C(8)	119.25(13)
O(1)-C(2)-C(4)	119.34(12)	O(3)-C(7)-C(6)	120.78(13)
C(5)-C(3)-C(9)	121.34(13)	C(8)-C(7)-C(6)	119.80(13)
C(5)-C(3)-C(1)	118.32(13)	C(11)-C(10)-C(4)	120.13(14)
C(9)-C(3)-C(1)	120.34(13)	C(10)-C(11)-C(12)	121.30(15)
C(10)-C(4)-C(14)	119.00(14)	C(13)-C(12)-C(11)	117.86(14)
C(10)-C(4)-C(2)	121.74(13)	C(13)-C(12)-C(15)	121.70(15)
C(14)-C(4)-C(2)	119.25(13)	C(1)-N(2)-N(1)	106.42(12)
C(6)-C(5)-C(3)	119.01(13)	C(1)-O(1)-C(2)	102.50(10)
O(2)-C(6)-C(5)	124.09(13)	C(6)-O(2)-C(16)	116.77(12)
O(2)-C(6)-C(7)	115.54(13)	C(7)-O(3)-C(17)	115.14 (12)

TABLE-3
ANTIBACTERIAL ACTIVITY OF THE TITLE COMPOUND

Compound	Concentration (mg/mL)	Diameter of inhibition zone (mm)	
		S. aureus	*E. coli*
Title compound	5.0	20.1	15.7
	2.5	18.3	14.3
	1.25	16.9	13.1
	0.625	16.0	12.1
DMF		7.8	7.8

the increase of the concentration in the test range. Besides, the title compound shows more abvious activity against *S. aureus* as compared to *E. coli*.

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