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Synthesis, Structure and Biological Activities of Novel Triazole Compounds Containing Ester Group

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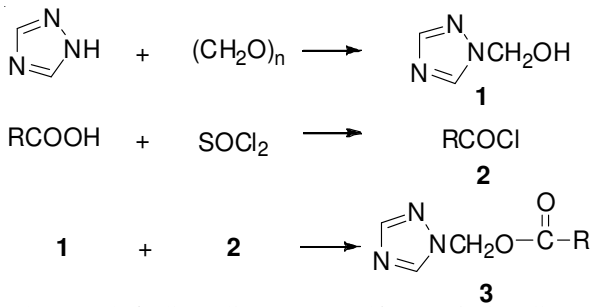
Novel triazole compounds containing ester group were synthesized. Their structure were confirmed by means of IR, ^{1}H NMR and elemental analysis. The single crystal structure of compound (1*H*-1,2,4-triazol-1-yl)methyl 3-(2,4-dichlorophenyl)propanoate (compound **3c**) was determined *via* X-ray diffraction. It crystallizes in a monoclinic system with space group P2(1)/c, a = 1.0814(2) nm, b = 0.64514(13) nm, c = 1.8698(4) nm, β = 101.05(3)°, Z = 4, V = 1.2802(5) nm^3, D_c = 1.557 Mg/m^3, μ = 0.508 mm^{-1}, F(000) = 616 and final R_1 = 0.0700. Intermolecular hydrogen-bond and π-π stacking interactions exit in the lattice, facilitating the stabilization of crystal structure. The results of the biological test show that these compounds have some fungicidal activity.

Keywords: Triazole, Ester group, Crystal structure, π-π Stacking, Biological activity.

INTRODUCTION

In studies on new pharmaceuticals and agrochemicals, heterocycles are worthy of very important consideration. Triazoles and their derivatives possess many pharmacological properties, such as an antiviral, anti-HIV-1, antimycobacterial, anticonvulsant, antimicrobial, antifungal, antitumor, antiinflammatory, fungicide, herbicide and plant growth-regulating activitie[1-8]. Meanwhile, phenoxyethanoic acid and its ester derivatives have effective biological activities[9-11]. For this reason, we designed (1*H*-1,2,4-triazol-1-yl) methanol as lead compounds, inducting ester group and phenoxyl, and synthesized six novel triazole compounds containing ester group so as to search for novel high activity compounds. The synthesis route is described in **Scheme-I**.



3a: R = 3,5-$(CH_3)_2C_6H_3$ 3b: R = 4-$C_2H_5C_6H_4$
3c: R = 2,4-$Cl_2C_6H_3(CH_2)_2$ 3d: R = 4-$BrC_6H_4OCH_2$
3e: R = 4-$NO_2C_6H_4OCH_2$ 3f: R = 4-$ClC_6H_4OCH_2$

Scheme-I: Synthesis reaction of target compounds

EXPERIMENTAL

All chemicals were obtained from a commercial source and used without further purification. Elemental analyses were measured with a Perkin-Elmer 1400C analyzer. IR spectra (4000-400 cm^{-1}), as KBr pellets, were recorded on a Nicolet FT-IR 170X spectrophotometer. ^{1}H NMR spectra were measured with a JEOL JNM-ECP600 nuclear magnetic resonance spectrometer ($CDCl_3$ as solvent, TMS as internal standard). The melting points were determined on a Yanaco MP-500 melting point apparatus.

Synthesis of target compounds: The intermediates **1** and **2** were prepared according to reference[12,13]. The synthesis of the target compounds is described as. To a 100 mL flask were added 10 mmol of intermediate **1** and 11 mmol of triethylamine in 20 mL of dry acetone, to which 10 mmol of intermediate **2** in 10 mL of acetone was then added dropwise with stirring fiercely in ice-cold water bath within 0.5 h. The reaction took place immediately and a lot of white solid appeared. The mixture was heated and refluxed for 2 h and then cooled to room temperature. After filtering and distilling under reduce pressure, a crude product was obtained.The crude product was purified by flash column chromatography (silica gel, using $V_{ethyl\ ethanoate}$:$V_{petroleum\ ether}$ = 1:3 as eluent) to afford the target compounds.

(1*H*-1,2,4-triazol-1-yl)methyl 3,5-dimethylbenzoate (3a): Yield: 75 %; m.p.: 105-107 °C: ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 8.48 (s, 1H, Tr-H), 7.99 (s, 1H, Tr-H), 7.66-7.22 (m, 3H, Ar-H), 6.29 (s, 2H, Tr-CH_2), 2.34 (s, 6H, 2CH_3). IR (KBr,

ν_{max}, cm^{-1}): 3118, 1721, 1515, 1200, 1108. Elemental anal. calc. (%) for $C_{12}H_{13}N_3O_2$ (M_r = 231.25): C 62.33, H 5.67, N 18.17; found (%): C 62.42, H 5.70, N 18.21.

(1*H*-1,2,4-Triazol-1-yl)methyl 4-ethylbenzoate (3b): Yield: 75 %; m.p.: 61-63 °C: ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 8.49 (s, 1H, Tr-H), 7.99 (s, 1H, Tr-H), 7.69-7.26 (m, 4H, Ar - H), 6.30 (s, 2H, Tr-CH_2), 2.71(q, 2H, Ar-CH_2), 1.25 (t, 3H, CH_3). IR (KBr, ν_{max}, cm^{-1}): 3101, 1717, 1514,1272, 1084. Elemental anal. calc. (%) for $C_{12}H_{13}N_3O_2$ (M_r = 231.25): C 62.33, H 5.67, N 18.17; found (%): C 62.45, H 5.72, N 18.26.

(1*H*-1,2,4-Triazol-1-yl)methyl 3-(2,4-dichlorophenyl)-propanoate (3c): Yield: 72.0 %; m.p.: 61-63 °C: ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 8.37 (s, 1H, Tr-H); 8.00 (s, 1H, Tr-H), 7.27-6.78 (m, 3H, Ar-H); 6.18 (s, 2H, Tr-CH_2), 4.66-4.65 (m, 4H, Ar-CH_2CH_2). IR (KBr, ν_{max}, cm^{-1}): 3125, 1738, 1516, 1252, 1092. Elemental anal. calc. (%) for $C_{12}H_{11}N_3O_2Cl_2$ (M_r = 300.14): C 48.02, H 3.69, N 14.00; found (%): C 48.13, H 3.73, N 14.38.

(1*H*-1,2,4-Triazol-1-yl)methyl 2-(4-bromophenoxy)-acetate (3d): Yield: 68.0 %; m.p.: 165-167 °C: ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 8.51 (s, 1H, Tr-H), 8.02 (s, 1H, Tr-H), 7.29-6.77 (m, 4H, Ar-H), 6.17 (s, 2H, Tr-CH_2), 4.67 (s, 2H, ArO-CH_2). IR (KBr, ν_{max}, cm^{-1}): 3132, 1728, 1510, 1269, 1089. Elemental anal. calc. (%) for $C_{11}H_{10}N_3O_3Br$ (M_r = 311.00): C 42.33, H 3.23, N 13.46; found (%): C 42.45, H 3.17, N 13.39.

(1*H*-1,2,4-Triazol-1-yl)methyl 2-(4-nitrophenoxy)-acetate (3e): Yield: 65.5 %; m.p.: 120-121°C: ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 8.40 (s, 1H, Tr-H), 8.03 (s, 1H, Tr-H), 7.42-6.74 (m, 4H, Ar-H), 6.30 (s, 2H, Tr-CH_2), 4.71 (s, 2H, ArO-CH_2). (KBr, ν_{max}, cm^{-1}): 3124, 1760, 1512, 1188, 1074. Elemental anal. calc. (%) for $C_{11}H_{10}N_4O_5$ (M_r = 278.07): C 47.49, H 3.62, N 20.14; found (%): C 47.40, H 3.71, N 20.08.

(1*H*-1,2,4-Triazol-1-yl)methyl 2-(4-chlorophenoxy)-acetate (3f): Yield: 86.5 %; m.p.: 146-150 °C: ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 8.37 (s, 1H, Tr-H), 8.00 (s, 1H, Tr-H), 7.27-6.78 (m, 4H, Ar-H), 6.17 (s, 2H, Tr-CH_2), 4.65 (s, 2H, ArO-CH_2). IR (KBr, ν_{max}, cm^{-1}): 3123, 1756, 1518, 1193, 1078. Elemental anal. calc. (%) for $C_{11}H_{10}N_3O_3Cl$ (M_r = 267.04): C 49.36, H 3.77, N 15.70; found (%): C 49.45, H 3.63, N 15.62.

X-ray crystallographic analysis: The single crystal of the compound **3c** was obtained from a methanol solution by slow evaporation at room temperature. The colorless crystal with the dimension 0.74 mm × 0.22 mm × 0.05 mm was selected for X-ray diffraction analysis. The data was collected by Rigaku R-axis Rapid IP Area Detector diffractometer using graphite monochromated MoK_α radiation (λ = 0.071073 nm), in the range 1.92° < θ < 27.36°, 2899 independent reflections were obtained.

The structure was solved by direct methods using SHELXS-97 program[14]. All the non-hydrogen atoms were refined on F^2 anistropically by full-matrix least squares method. Hydrogen atoms were located from the difference Fourier map and added to the structure calculation, but their positions were not refined. The contributions of these hydrogen atoms were included in structure-factor calculations. The final least-square cycle gave R_1 = 0.0700, ωR_2 = 0.2202 for 2185 reflections with $I > 2\sigma(I)$; The weighting scheme, $\omega = 1/[\sigma^2 (F_o^2) + (0.1466P)^2 + 1.164P]$, where $P = (F^2_o + 2F^2_c)/3$. The maximum and minimum difference peaks and holes are 1360 e/nm^3 and -753 e/nm^3, respectively. S = 1.062 and $(\Delta/s)_{max}$ = 0.006. Atomic scattering factors and anomalous dispersion correction were taken from International Table for X-Ray Crystallography[15]. A summary of the key crystallographic information is given in Table-1.

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR THE COMPOUND **3c**

Empirical formula	$C_{12}H_{11}N_3O_2Cl_2$
m.w.	300.14
Crystal systerm	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 1.0814(2) nm α = 90º
	b = 0.64514(13) nm β = 101.05(3)º
	c = 1.8698(4) nm γ = 90º
Volume	1.2802(4) nm^3
Z, Calculated density	4, 1.557 Mg/m^3
Absorption coefficient	0.508 mm^{-1}
Crystal size	0.74 × 0.22 × 0.05 mm
F(000)	616
θ angle for data collection	1.92º to 27.36º
Limiting indices	$-13 \le h \le 3$, $-8 \le k \le 8$, $-24 \le l \le 23$
Reflections collected/ unique	11868 / 2899 [R(int) = 0.0427]
Data/restraints/parameters	2899 / 0 / 172
Final R indices [I>2σI)]	R_1 = 0.0700, wR_2 = 0.2202
Largest diff. peak and hole	1360 e/nm^3 and -753 e/nm^3

RESULTS AND DISCUSSION

Design idea of the target compounds: The triazole compounds inducting ester group, reported in literature[16-18], are mostly oxime esters that are prepareed by means of α-triazolyl ketoxime reacting with acyl chloride. Also, some of them are obtained *via* triazole reacting with halogenated aliphatic ester.

We made (1*H*-1,2,4-triazol-1-yl)methanol (intermediates **1**) react with aryl chlorides (intermediates **2**) to get six novel triazole compounds containing ester group. The structure of the synthetical compounds is reported for the first time although the synthesis method is classical.

Spectral characterization of the target compounds: The ^{1}H NMR, IR, elemental analysis results for the target compounds are good agreement with their structure. In the IR spectrum, there are medium or weak absorption bands for the benzene ring and the triazole ring at 3100 cm^{-1}. The strong absorption at 1760-1717, 1272-1188 and 1108-1074 cm^{-1} are attributed to C=O and C-O-C stretching vibration absorption in the ester group, respectively. In the ^{1}H NMR spectrum, the chemical shifts for the two protons of the triazole ring appears at 8.51-8.37 and 8.03-7.99, respectively. The chemical shifts for the two protons of the CH_2 group connecting with a triazole ring at 6.30-6.17. The chemical shifts for the protons of the benzene ring at 7.69-6.74.

Description of the crystal structure of the compound 3c: Fig. 1 and 2 show the molecular structure and the perspective view of the crystal packing in the unit cell of the compound **3c**. The selected bond lengths, angles and hydrogen-bonding geometry of compound 3c are listed in Tables 2 and 3, respectively.

The compound of **3c** crystallizes as monoclinic system. The bond lengths and angles are generally normal in the phenyl

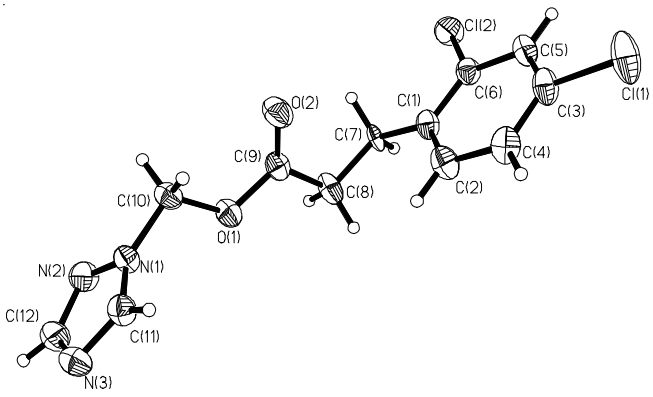


Fig. 1. Molecular structure for compound **3c**

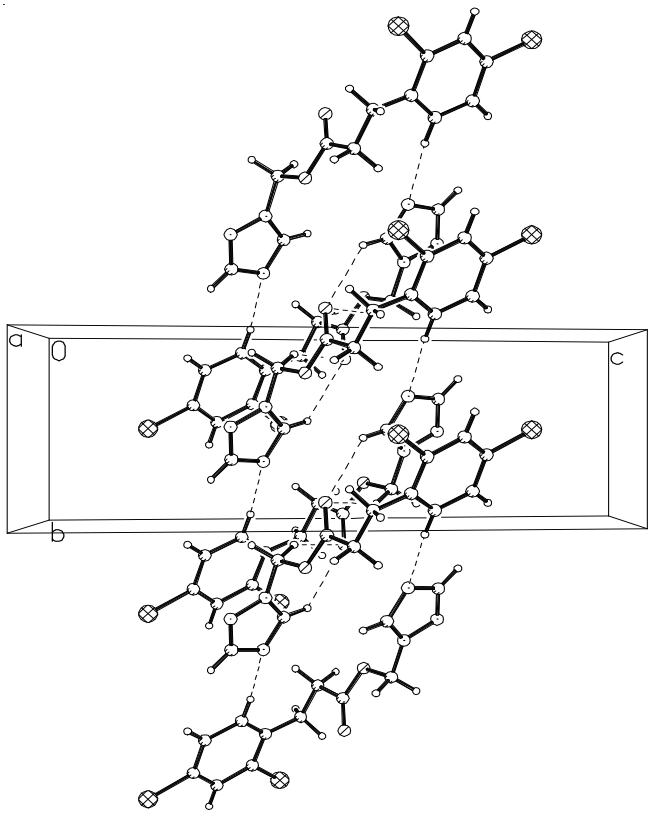


Fig. 2. View of the crystal packing down the b axis for compound **3c**

TABLE-2
SELECTED BOND LENGTHS (NM) AND ANGLES (º) FOR COMPOUND **3c**

C(7)–C(8)	0.1423(4)	C(8)-C(9)	0.1515(5)
O(2)–C(9)	0.1201(4)	O(1)-C(9)	0.1335(4)
O(1)-C(10)	0.1441(4)	N(1)-C(10)	0.1435(4)
O(2)-C(9)-C(8)	126.2(3)	N(2)-N(1)-C(10)	120.9(3)
O(2)-C(9)-O(1)	124.2(3)	C(11)-N(1)-C(10)	128.9(3)
O(2)-C(10)-N(1)	107.6(3)	C(7)-C(8)-C(9)	111.0 (3)
C(1)-C(7)-C(8)	119.5(3)	C(7)-C(1)-C(2)	124.6(3)

and triazole rings[19]. The C-O bond length of 0.1441(4) nm is shorter than the similar structure C-O length (0.1474(9) nm)[20]. The triazole ring with the atom C(10) are fairly planar (plane p1) with plane equation 0.6541x -0.4256y + 0.6253z = 2.1310. The atoms C(8), C(9), C(10), O(1) and O(2) form another plane(p2). The dihedral angles formed by p1 and p2 is 77.32 º.

In the lattice, there are some intermolecular and π-π stacking interactions. The π-π stacking interactions take place between the ring of 2,4-dichlorophenyl and the ring of triazol, with a separation of 0.375 nm. All above hydrogen bonds in this structure form the three dimensional hydrogen bonds network which stabilizes the crystal structure of **3c**.

Biological activity: We studied the fungicidal activities of the target compounds against *F. graminerum*, *A. solani*, *P. asparagi*, *B. berengeriana*, *C. archidicala* at 50 μg/mL by means of the poison contained in the medium[21]. The experimental results are shown in Table-4. All of the title compounds have some fungicidal activities. Compounds **3a** exhibit a better efficiency on the above five tested germs. The six compounds all show inhibiting activity towards *B. Berengeriana*. The inhibiting rates of compound **3a-3f** reached 56.1 % at 50 μg/mL at most. They all have a lower inhibition rate against *C. archidicola*. We'll study its fungicidal activities for other diseases and explore their efficiency value further.

Conclusion

Using (1*H*-1,2,4-triazol-1-yl)methanol as the lead compound, inducting ester group and phenoxyl, we synthesized six novel triazole compounds containing ester group. Their structure were confirmed by means of IR, ^{1}H NMR and elemental analysis. The single crystal structure of compound (1*H*-1,2,4-triazol-1-

TABLE-3
INTERMOLECULAR INTERACTION DISTANCES (NM) OF COMPOUND **3c**

D H A	symm	D-H	H···A	D···A	D-H···A
C(2)-H(2A)···N(3)	1-x,-y,-z	0.093	0.245	0.33590	16.4
C(7)-H(7A)···O(2)	2-x,-1/2+y,1/2-z	0.097	0.274	0.35782	14.5
C(10)-H(10B)···O(2)	1-x,1-y,-z	0.097	0.253	0.33894	14.7
C(11)-H(11A)···O(2)	1-x,1-y,-z	0.093	0.254	0.32907	13.8

TABLE-4
FUNGICIDAL ACTIVITIES OF COMPOUND **3a-3f**

Compound	Fungicidal activities (50 μg/mL, inhibition %)				
	F. graminerum	*A. solani*	*P. asparagi*	*B. berengeriana*	*C. archidicola*
3a	24.3	29.4	18.8	44.6	10.0
3b	16.2	20.6	0	44.6	15.0
3c	0	17.7	12.5	44.6	0
3d	12.8	12.9	35.3	50.0	11.1
3e	41.0	25.8	0	56.1	33.3
3f	17.9	25.8	29.4	47.0	18.5

yl)methyl 3-(2,4-dichlorophenyl)propanoate (compound **3c**) was determined *via* X-ray diffraction. It crystallizes in a monoclinic system with space group P2(1)/c, a = 1.0814(2) nm, b = 0.64514(13) nm, c = 1.8698(4) nm, β = 101.05(3)°, Z = 4, V = 1.2802(5) nm^3, D_c = 1.557 Mg/m^3, μ = 0.508 mm^{-1}, F(000) = 616 and final R_1 = 0.0700. Intermolecular hydrogen-bond and π-π stacking interactions exit in the lattice, facilitating the stabilization of crystal structure. The results of the biological test show that these compounds have certain fungicidal activity although it is not very good. The target compounds exhibit better fungicidal activity against *B. berengeriana*, reach 56.1 % at most.

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