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Crystal Structure Analysis of Ethyl 7-Phenyl-5-*p*-tolylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate

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The title compound, $C_{22}H_{19}N_3O_2$, was prepared from the three-component reaction. The structure of the title compound was established by single-crystal X-ray diffraction. The molecular structure shows that the phenyl ring is not coplanar with the pyrimidine ring. The torsion angle between the phenyl ring and pyrimidine ring is 147.01(15)°. The glide related molecules form one-dimensional corrugated tape-like structure via C–H···O hydrogen bonds along the crystallographic b-axis. These one-dimensional layers stack along the a-axis and form a corrugated layered structure and these layers are further stabilized by the weak C–H···π interactions. Also, it was found that the pyrazole moiety and p-toluyl groups of glide-related molecules are stacked through π···π interactions.

Keywords Pyrazolopyrimidines; single crystal; X-ray; hydrogen bonding

Introduction

Pyrazole and pyrimidine derivatives attracted organic chemists very much due to their biological and chemotherapeutic importance. The heterocyclic fusion of pyrimidine ring and pyrazole ring resulted in formation of pyrazolopyrimidines. Recently, pyrazolopyrimidines that belongs to this class have attracted considerable interest because of their remarkable pharmacological properties [1–4]. In recent years, pyrazolopyrimidines and related fused heterocycles have been identified as bioactive molecules. They are known to function as Central Nervous System depressants, neuroleptic agents, tuberculostatic, antiallergic, and antileishmanial activity, adenosine receptor inactivation in a model of Parkinson's disease, hypotensive activities, anti-inflammatory activity, and antitumor and bacteriostatic agents

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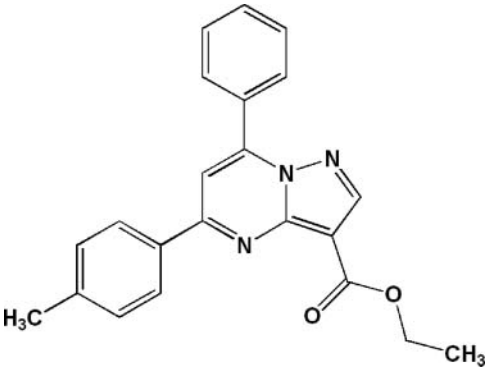


Figure 1. Molecular structure of the compound-**1**.

[5–12]. These results prompted us to synthesize the title compound of novel pyrazolopyrimidine derivative containing a pyrazole and pyrimidine ring. In a continuation of our study about synthesis and reactivity of pyrazolo pyrimidines [13], we reported, in this communication, the title compound, ethyl 7-phenyl-5-p-tolylpyrazolo[1,5-a]pyrimidine-3-carboxylate has been synthesized by our reported procedure [13d] and its structure was determined using the single crystal X-ray diffraction method and characterized with spectroscopic techniques. The structure of ethyl 7-phenyl-5-p-tolylpyrazolo[1,5-a]pyrimidine-3-carboxylate molecule is given in Fig. 1. In this context, we now wish to present the detailed crystal structure analysis based on X-ray diffraction.

Materials and Methodology

General Procedures and Materials

Reaction was carried out under nitrogen atmosphere. Melting points were determined on a Buchi B-540 melting point apparatus and are uncorrected. All compounds were routinely checked by Thin Layer Chromatography (TLC) and ^{1}H NMR.< TLC was performed on aluminum-backed silica gel plates (Merck DC, Alufolien Kieselgel 60 F254) with spots visualized by UV light. All chemicals and reagents (purity >99.8%) were purchased from Aldrich Co. Ltd, Bangalore, India.

^{1}H and ^{13}C NMR Spectroscopy

^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ solution using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.0$) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz.

Infrared Spectroscopy

Jasco FT–IR 4200 (Easton, Maryland) type-A Fourier transform infrared spectrophotometer was used to record the Infrared spectroscopy (IR) spectra of the samples (sample concentration is 2 mg in 20 mg of KBr). The spectra were recorded over the range of

4000–600 cm^{-1}. Data were analyzed using spectrum version 2 software (JASCO, Easton, Maryland, USA).

High Resolution Mass Spectra

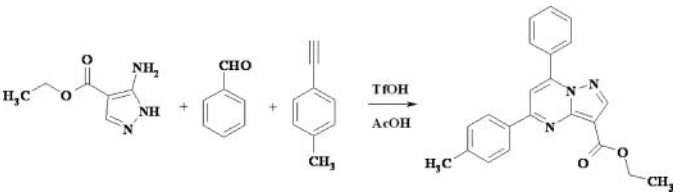
High-resolution mass spectra (HRMS) were measured on a Waters LCT Premier XE instrument.

Single-Crystal X-ray Diffraction

The single-crystal X-ray diffraction data of the crystals were collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 296(2) K using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). No absorption correction was applied. The lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program SHELXTL [14]. The crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97 [15]. The positions of all aromatic and aliphatic C–H hydrogen atoms were calculated geometrically, and a riding model was used in the refinement, with C–H distances in the range of 0.93–0.98 Å and Uiso(H) = 1.5Ueq(C). The software used to prepare material for publication was Mercury 2.3 (Build RC4), ORTEP-3, and X-Seed [16]. Table 1 gives the pertinent crystallographic data, and Table 2 gives hydrogen bond parameters.

Results and Discussion

For the synthesis (Scheme 1), a mixture of ethyl 5-amino-1*H*-pyrazole-4-carboxylate (1.0 mmol), benzaldehyde (1 mmol), and 1-ethynyl-4-methylbenzene (1 mmol) in acetic acid (5 mL) was stirred at 25°C for 10 min. To this clear solution was added triflic acid (10 mol%) and the mixture was heated to 100°C–110°C. The reaction mixture was then stirred at same temperature for 2 h. After completion of the reaction the mixture was cooled to room temperature, poured into ethyl acetate (25 mL) and washed with brine solution (2 × 15 mL) followed by 10% sodium bicarbonate solution (2 × 15 mL). The organic layer was collected, dried over anhydrous Sodium sulphate and concentrated. The crude product was crystallized from dimethylformamide (DMF) and compound-**1** was obtained as colorless needles by slow evaporation. M.p. 120°C–122°C; yield 80%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.58 (s, 1H, CH), 8.20 (d, $J = 8.3$ Hz, 2H, CH), 8.04–8.01 (m, 2H, CH), 7.63–7.60 (m, 3H, CH), 7.50 (s, 1H, CH), 7.35 (d, $J = 8.3$ Hz, 2H, CH), 4.47 (q, $J = 7.3$ Hz, 2H, OCH_2), 2.45 (s, 3H, CH_3), 1.48 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 158.9, 148.9, 147.6, 141.6, 133.7, 131.2, 130.7, 129.6, 129.4, 128.7, 127.5, 106.1, 102.8,



Scheme 1. Synthetic route for the compound-**1**.

Table 1. Salient crystallographic data and structure refinement parameters of compound-**1**

	1
Empirical formula	$C_{22}H_{19}N_3O_2$
Formula weight	357.4
Crystal system	Orthorhombic
Space group	*Pbca*
T/K	273(2)
a/Å	8.0771(7)
b/Å	17.3487(19)
c/Å	25.486(3)
α/°	90
β/°	90
γ/ °	90
Z	2
V/Å^3	3571.3(7)
D_{calc}/g/cm^3	1.329
F(000)	1504.0
μ/mm^{-1}	0.087
θ/°	2.36–26.99
Index ranges	$-9 \leq h \leq 5$ $-20 \leq k \leq 20$ $-30 \leq l \leq 30$
N-total	29175
N-independent	3168
N-observed	2531
Parameters	247
Rint	0.0459
R_1 ($I > 2\sigma(I)$)	0.0355
wR_2 (all data)	0.0836
GOF	1.063
CCDC	900956

60.1, 21.4, 14.5; IR (KBr): 2982, 1686, 1606, 1556 cm^{-1}; and HRMS (ESI): calcd for $C_{22}H_{20}N_3O_2$ $(M+H)^+$ 358.1556, found 358.1543.

Crystal Structure Analysis

The compound-**1** crystallizes in the centrosymmetric orthorhombic *Pbca* space group with one molecule in the asymmetric unit (Fig. 2). The crystal structure analysis reveals that the molecules form corrugated layers with C–H···O hydrogen bonds. The molecular structure shows the p-toluyl group is essentially coplanar with the pyrimidine ring. But the phenyl ring is not coplanar with the pyrimidine ring. The torsion angle between the phenyl ring and pyrimidine ring (N2–C3–C16–C21) is 147.01(15)°. The glide related molecules form one-dimensional

Table 2. Geometrical parameters of hydrogen bonds in compound-1

Compound	D–H···A[a]	D···A (Å)	H···A (Å)	D–H···A (°)	Symmetry code
1	C(9)–H(9A)···O(1)	3.719(2)	2.91	132	−1/2+x,y,1/2-z
	C(9)–H(9C)···N(2)	3.694(2)	2.74	146	1/2+x,y,1/2-z
	C(9)–H(9C)···N(3)	3.704(2)	2.84	137’	1/2+x,y,1/2-z
	C(11)–H(11)···O(1)	3.582(2)	2.99	115	−x,1/2+y,1/2-z
	C(12)–H(12)···O(1)	3.390(2)	2.55	133	−x,1/2+y,1/2-z
	IntraC(17)–H(17)···N(3)	2.941(2)	2.39	110	–
	C(18)–H(18)···N(3)	3.408(2)	2.64	127	−1/2+x,1/2-y,1-z
	C(19)–H(19)···N(3)	3.495(2)	2.84	119	−1/2+x,1/2-y,1-z
	C(21)–H(21)···O(1)	3.757(2)	2.68	173	1/2-x,1/2+y,z

[a]All of the C–H distances are neutron normalized to 1.083 Å.

corrugated tape-like structure via C–H···O hydrogen bonds [C(12)···(O1) = 3.390(2) Å, C(12)–H(12)···O(1) = 133°] along the crystallographic *b*-axis. These one-dimensional layers stack along the *a*-axis and form a corrugated layered structure (Fig. 3) and these layers are stabilized by the weak C–H···$\pi_{centroid}$ [C(14)–H(14)···$\pi_{C16–C17–C18–C19–C20–C21}$; C···$\pi_{centroid}$ = 3.4499(18); C–H···$\pi_{centroid}$ = 2.92 Å, 151.55°] and $\pi_{centroid}$···$\pi_{centroid}$ stacking [$\pi_{(C10–C11–C12–C13–C14–C15)}$··· $\pi_{(C4–C5–C6–N3–N2)}$ = 3.5454(10) Å] interactions.

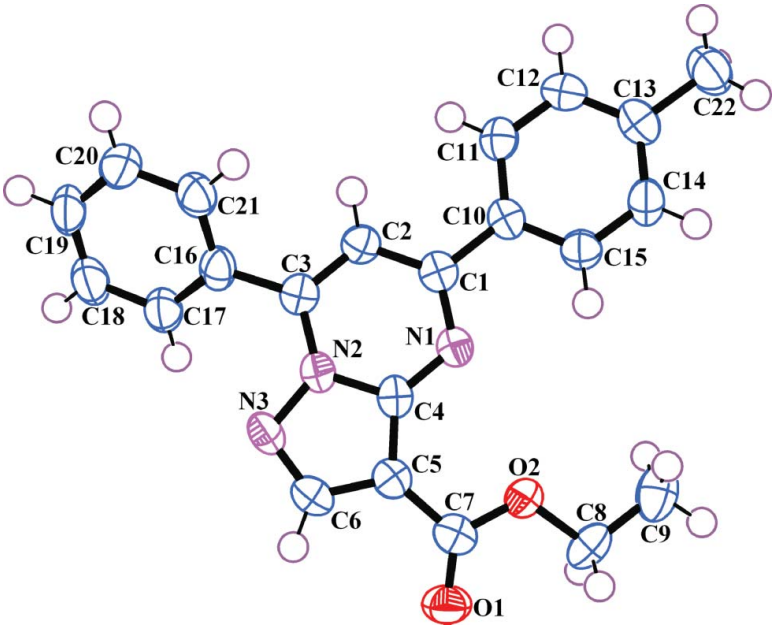


Figure 2. ORTEP representation of the compound-**1**. (Thermal ellipsoids are drawn at 90% probability level.)

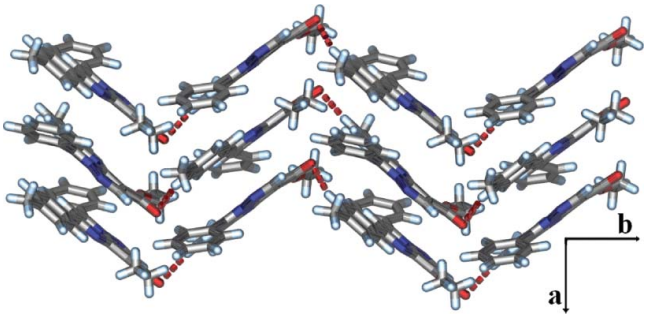


Figure 3. Crystal packing of compound-**1**: showing the corrugated layers formed with C–H···O hydrogen bonds along the crystallographic *b*-axis. These layers are stabilized by the weak C–H···$\pi_{centroid}$ and $\pi_{centroid}\cdots\pi_{centroid}$ interactions.

Conclusions

The compound-**1** was prepared and its molecular structure was confirmed by IR, ^{1}H and ^{13}C NMR, and HRMS spectroscopy. Finally, the crystal structure was established by single-crystal X-ray diffraction. The molecules form one-dimensional corrugated tape-like structure via C–H···O hydrogen bonds. The over all structure is a corrugated layered structure and these layers are further stabilized by the weak C–H···π interactions.

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