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Crystal structure and synthesis of 4-(4-hydroxybenzylideneamino)-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide

D. Rambabu [a], G. Rama Krishna [b], Srinivas Basavoju [c], C. Malla Reddy [b,*], Manojit Pal [a,*]

[a] Institute of Life Sciences, University of Hyderabad Campus, Hyderabad 500 046, Andhra Pradesh, India
[b] Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal 741 252, India
[c] Department of Chemistry, National Institute of Technology (NIT), Warangal 506 004, Andhra Pradesh, India

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ABSTRACT

The title compound $C_{15}H_{18}N_4O_2$ (**I**), was prepared from the reaction of 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide and 4-hydroxybenzaldehyde; and was analyzed by analytical data from ^{1}H NMR, ^{13}C NMR, IR and Mass spectra. The crystal structure was determined by single crystal X-ray diffraction. The molecules in the crystal structure form cyclic centrosymmetric supramolecular tetramer synthons [graph-set $R_4^4(12)$] through amide N–H···O(hydroxy) and hydroxy O–H···O(amide) hydrogen bonds to form perpendicular tapes.

1. Introduction

Many natural products have the pyrazole unit as the core structure [1]. Pyrazole derivatives exhibit important biological properties such as antitumour [2], anticoagulant [3], anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, hypoglycemic and sedative–hypnotic activity [4–6]. These derivatives have attracted significant attention because of the application in drug development [7]. Particularly, arylpyrazoles are important in medicinal and pesticidal chemistry [8]; a number of herbicides with pyrazole moieties have been commercialized [9]. Recent literature shows that, some arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity [10]. Recently Tang et al. reported the synthesis and crystal structure of a pyrazole derivative [11]. It is also reported that novel five-substituted pyrazole analogs, which have CB1 binding affinities similar to SR 141716A have been synthesized [12]. Wei et al. investigated effects of pyrazole-5-carboxylate derivatives on A549 cell growth and suppress this growth [13].

Compounds containing carboxamide and benzylideneamino group at the adjacent positions of a five-membered heterocyclic ring are of considerable interest due to their interesting pharmacological properties [14,15]. For example Schiff bases derived from benzaldehydes with 3-amino-2-benzofurancarboxamide were evaluated for antibacterial and anthelmentic properties [15]. In our effort to identify pyrazole-based novel antibacterial agents we prepared a series of 4-benzylideneamino-pyrazole-5-carboxamide for our in house in vitro screen. Among the compounds synthesized 4-(4-hydroxybenzylideneamino)-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**I**) was identified as a key compound in this series. In this paper we describe the synthesis and crystal structure analysis of this compound.

2. Results and discussion

The title compound was prepared (Scheme 1) by the reaction of a mixture of 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide **(1)** (1.0 mmol), 4-hydroxybenzaldehyde **(2)** (1.0 mmol) and Amberlist (10 mg). The reaction mixture was stirred in acetonitrile (10 mL) at room temperature for 2 h. After completion of the reaction, the solid product was filtered and dried. The crude product was crystallized from methanol and colorless needle shaped crystals were obtained on slow evaporation (yield: 80%). The analytical data (^{1}H NMR, ^{13}C NMR, IR and Mass spectra) of this compound are available in supplementary information as Figs. S1–S4.

The X-ray data for crystals of the compound (**I**) were collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 296(2) K using graphite-monochromated Mo Kα radiation (λ = 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 [16a]. The structure was solved by direct methods using SHELXS-97 and refined by full-ma-

* Corresponding authors. Mobile: +91 9000015358 (M. Pal).
E-mail addresses: cmallareddy@rediffmail.com (C.M. Reddy), manojitpal@rediffmail.com (M. Pal).

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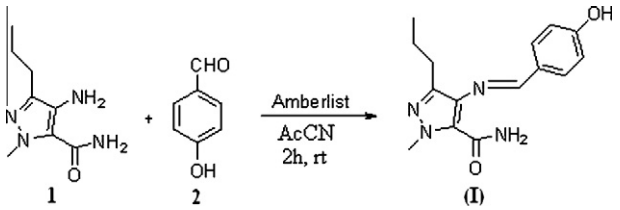

Scheme 1. Synthesis of 4-(4-hydroxybenzylideneamino)-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**I**).

Table 1
Crystallographic data and refinement parameters of compound (**I**).

Empirical formula	$C_{15}H_{18}N_4O_2$
Formula weight	286.33
Crystal system	Monoclinic
Space group	$P2_1/n$
T (K)	296(2)
a (Å)	8.0008(6)
b (Å)	10.1498(7)
c (Å)	17.9367(13)
α (°)	90.00
β (°)	98.534(3)
γ (°)	90.00
Z	4
V (Å^3)	1440.45(18)
D_x (g/cm^3)	1.320
Radiation	Mo Kα (λ = 0.71073 Å)
μ(Mo Kα)/mm^{-1}	0.091
F(0 0 0)	608.0
Crystal size/mm	0.28 × 0.20 × 0.18
θ range for data collection (°)	2.36–26.99
Limiting indices	$-8 \leqslant h \leqslant 9$, $-12 \leqslant k \leqslant 11$, $-20 \leqslant l \leqslant 19$
Reflections collected	25,563
Data/restraints/parameters	2575/0/202
Unique reflections	2575
Observed reflections	1937
Goodness-of-fit on F^2	1.081
R indices $I > 2\sigma(I)$	R_1 = 0.0470, wR_2 = 0.1153
R indices (all data)	R_1 = 0.0565, wR_2 = 0.1236
$(\Delta/\sigma)_{max}$	0.011
$(\Delta/\rho)_{max}$ (e Å^{-3})	0.30
Measurement	Bruker APEX-II CCD
Programs system	SHELXTL-97
Structure determination	SHELXS-97
CCDC deposition number	804,566

Table 2
Hydrogen bond parameters in compound (**I**).

Interaction	H···A (Å)	D···A (Å)	D–H···A (°)[a]	Symmetry code
Intra N(4)–H(4B)···N(3)	2.07(2)	2.808(2)	138.2(19)	–
N(4)–H(4A)···O(2)	2.15(3)	3.007(2)	164(2)	1/2 − x, 1/2 + y, 1/2 − z
O(2)–H(2)···O(1)	1.68(3)	2.634(2)	171(2)	1/2 + x, 3/2 − y, −1/2 + z

[a] All the N–H and O–H distances are neutron-normalized to 1.009 and 0.983 Å, respectively.

trix least squares on F^2 with anisotropic displacement parameters for non-H atoms, using SHELXL-97 [16b]. 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) = 1.2Ueq(C). All the N–H and O–H hydrogens were refined from difference Fourier maps. The software used to prepare material for publication was Mercury 2.3 (Build RC4), ORTEP-3 and X-Seed [17]. Table 1 summarizes the pertinent crystallographic data and Table 2 gives the hydrogen-bond geometries.

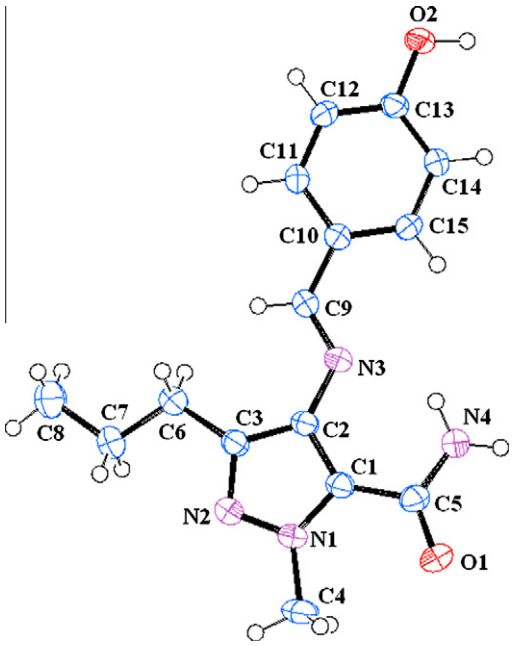

Fig. 1. ORTEP representation of compound (**I**). Thermal ellipsoids are drawn at 50% probability.

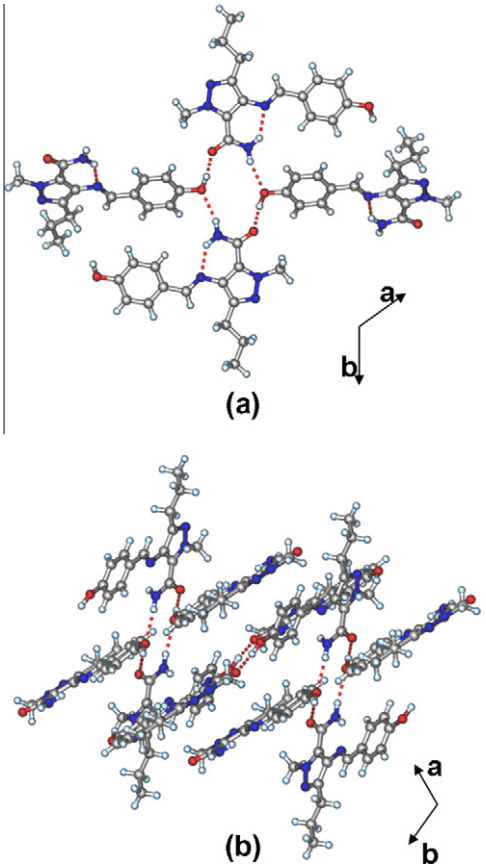

Fig. 2. (a) A tetramer synthon is formed *via* N–H···O and O–H···O hydrogen bonds in the crystal structure of compound (**I**). (b) Molecules forming perpendicular tapes in compound (**I**).

The compound (**I**) crystallizes in the monoclinic $P2_1/n$ space group with one molecule in the asymmetric unit ($Z' = 1$) (Fig. 1). The 4-hydroxybenzylidene and amide groups in the molecule are essentially coplanar with the pyrazole moiety (torsion angles: C1–C2–N3–C9 = 174.88°; N1–C1–C5–N4 = 175.34°). The crystal structure analysis reveals that the molecules in the crystal form perpendicular tapes. The *anti*-N–H group of amide group moiety form an intramolecular N–H···N ($D = 2.808(2)$ Å, $\theta = 138.2(19)°$) hydrogen with imine N-atom of 4-hydroxybenzylideneamine (Fig. 2a). It is surprising that the amide groups in the crystal do not form robust head-to-head amide dimer homosynthons, instead, four molecules of the compound (**I**) form a centrosymmetric cyclic supramolecular tetramer (graph-set $R_4^4(12)$) synthon (Fig. 2a) [18]. The two *syn*-N–H groups of two amide groups of a pair of molecules and two hydroxy groups of two 4-hydroxybenzylidene moieties of another pair of molecules form the tetramer *via* N–H···O ($D = 3.007(2)$ Å, $\theta = 164(2)°$) and O–H···O ($D = 2.634(2)$, $\theta = 171(2)°$) hydrogen bonds to form perpendicular tapes (Fig. 2b).

3. Conclusions

The compound (**I**), 4-(4-hydroxybenzylideneamino)-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide was synthesized and confirmed by ^{1}H NMR, ^{13}C NMR, IR and Mass spectral data. Its crystal structure was determined by single crystal X-ray diffraction. The crystal structure was described in terms of supramolecular tetramer synthons and found perpendicular tapes.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2011.03.045.

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