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RESEARCH ARTICLE

Structural investigation of 1-Phenyl-3-(3-methyl-2-benzoxazolinone-6-yl)-1H-pyrazole-4-carboxy aldehyde

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Structural investigation of 1-Phenyl-3-(3-methyl-2-benzoxazolinone-6-yl)-1H-pyrazole-4-carboxy aldehyde

Summary

1-Phenyl-3-(3-methyl-2-benzoxazolinone-6-yl)-1H-pyrazole-4-carboxyaldehyde was prepared and its structure was confirmed by elemental analysis, IR and NMR spectroscopic analyses. Also, its crystal structure was investigated by x-ray diffraction. The stability of the molecule in the crystal lattice was elucidated by the inter and the intra-molecular C-H…O interactions.

Key Words: *Chemical synthesis, X-ray diffraction, Crystal structure.*

1-Fenil-3-(3-metil-2-benzoksazolinon-6-il)-1H-prazol-4-karboksi aldehit yapısının incelenmesi

Özet

1-Fenil-3-(3-metil-2-benzoksazolinon-6-il)-1H-prazol-4-karboksialdehit sentezlendi ve yapısı elementel analiz, IR ve 1H-NMR spektroskopik analizleri ile aydınlatıldı. Aynı zamanda bileşiğin kristal yapısı da x-ray difraksiyon ile incelendi. Kristal yapıdaki bileşiğin kararlılığı molekül içi ve moleküller arası C-H…O etkileşimleri ile açıklandı.

Anahtar Kelimeler: *Kimyasal sentez, X-ray difraksiyon, Kristal yapı*

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INTRODUCTION

For the purpose of developing a novel anti-inflammatory drug candidate with less cardiac side effects, 1-phenyl-3- (3-methyl-2-benzoxazolinone-6-yl) -1H-pyrazole-4-carboxy aldehyde was designed and synthesized under the Vilsmeier-Haack reaction conditions (1) as an initial compound to achieve some potent 1,3-diaryl substituted 1H-pyrazole derivatives as dual inhibitors of cyclo-oxygenase and thromboxane synthase enzymes, as previously reported by Unlu *et al.* (2).

EXPERIMENTAL

All chemicals and solvents used were of reagent grade (Merck or Aldrich), and were used without further purification. Thin layer chromatographic (TLC) analyses were performed on the pre-coated aluminum plates (silica gel 60 F254, Merck). The TLC spots were visualized under the UV light. The elemental analyses, and the development of the NMR spectra were performed in the Central Laboratory of the Faculty of Pharmacy, Ankara University.

Synthesis

$POCl_3$ (0.003 mol) was added drop wise to an ice-cold continuously stirred solution of phenyl hydrazone of 3-methyl-6-acetyl-2 (3*H*) -benzoxazolone (0.001 mol) in DMF. The reaction mixture was allowed to reach the room temperature and then refluxed at 70-80° C for 4 h. The resulting mixture was poured onto crushed ice, neutralized with diluted sodium hydroxide and left standing overnight. The yellow precipitate obtained was purified via crystallization in toluene.

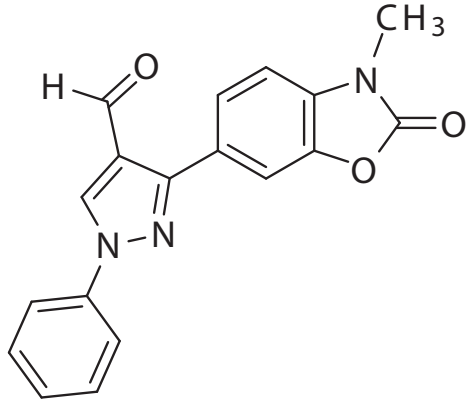

Figure 1. Chemical structure of the title compound.

Chemical characterization

The elemental analysis were performed on a Leco CHNS 932 analyzer and satisfactory results within the ±0.4% range of the theoretical values (C, H, N) were obtained with the following outcomes (theoretical%/ experimentally confirmed%); $C_{18}H_{13}N_3O_3$ C = 67.71/67.67; H = 4.10/4.11 and N = 13.16/13.21. The IR spectra were recorded in KBr pellets on a Bruker 1000 FTIR spectrometer in the range of 4000-400 cm^{-1} with the following IR ν_{max} cm^{-1} (KBr): 3120 (C-H, aromatic), 2720 (C-H stretch, aldehydic), 1760 (C = O, lactam), 1688 (C = O, aldehyde). The NMR spectra were detected by a Varian Mercury 400 FT-NMR spectrometer using $CDCl_3$ as a carrier medium. All chemical shifts were reported as δ (ppm) values with following results;

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.54 (s, 1H), 7.78 (m, 4H), 7.53 (t, 2H, *J* = 8.0), 7.41 (t, 1H, *J* = 7.6), 7.08 (d, 1H, J = 8.0), 3.47 (s, 3H).

X-ray characterization

For the x-ray measurements, the data collection was carried out on a crystal measuring 0.06 × 0.09 × 0.45 mm using Enraf-Nonius CAD4 diffractometer utilizing mono-chromated MoKα radiation. The relevant data for the crystal are listed in Table 1. The unit cell dimensions were determined from the angular settings of 25 reflections; and a total of 1828 reflections were measured. The structure was resolved by the SHELXS-86 software (3) and refined by the SHELXL-97 software (4).

RESULTS and DISCUSSION

Crystal structure description

The final atomic coordinates and equivalent thermal parameters for all of the non-hydrogen atoms are given in Table 2. The selected bond lengths, angles and torsion angles of all non-hydrogen atoms having a good agreement with the standard values, are given in Table 3. CCDC 696333 contains the supplementary crystallographic data for this study. These data can be obtained free of charge from the Chambridge Crystallographic Data Centre. Fig. 2 represents an ORTEP (5-6) diagram of the molecule with the thermal ellipsoids drawn at a probability of 30%.

Table 1. Crystal details and experimental data

Chemical Formula	$C_{18}H_{13}N_3O_3$	
Formula weight (amu)	319.32	
Crystal	yellow prism	
Crystal size (mm)	0.06 × 0.09 × 0.45	
Crystal system	Triclinic	
Space group; *Z*	P-1; 2	
Unit cell parameters	*a* = 8.0366 (6) Å	α = 99.787 (9)°
	b = 9.6546 (12) Å	β = 96.960 (7)°
	c = 10.5640 (9) Å	γ = 109.034 (9)°
Cell volume *V* (Å^3)	749.72 (13)	
D_x (g/cm^3)	1.415	
λ (MoK_α) Å	0.71073	
μ (MoK_α) mm^{-1}	0.099	
T (K)	293 (2)	
F (000)	332	
θ_{max}	21.94°	
Number of reflections measured	1828	
Number of reflection [*I* >2 (*I*)]	810	
Number of parameters	217	
R and *Rw* values	0.0613; 0.1690	
Goodness of fit	0.834	
$(\Delta/\sigma)_{max}$	0.060	
$(\Delta\rho)_{max}$	0.272 eÅ^{-3}	
$(\Delta\rho)_{min}$	-0.260 eÅ^{-3}	
Measurements	Enraf-Nonius CAD-4 diffractometer	
Program system	CAD-4-EXPRESS software	
Structure determination	direct method (SHELXS-86)	
Refinement	full matrix least-squares (SHELXL-97)	
Treatment of hydrogen atoms	geometric calculation	

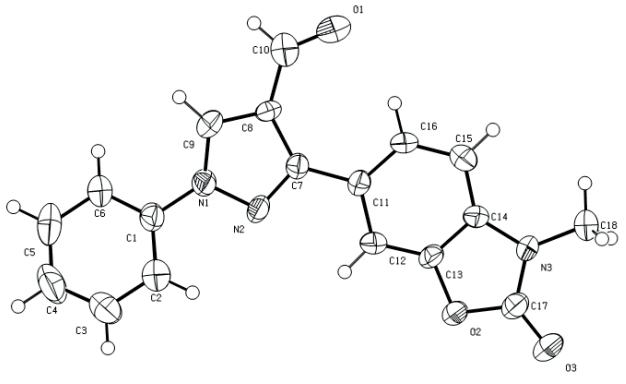

Figure 2. An ORTEP drawing of molecular structure with the crystallographic numbering scheme. Thermal ellipsoids are drawn at 30% probability level.

Table 2. Fractional atomic coordinates and equivalent displacement parameters $U_{eq} = (1/3) \sum_i \sum_j \boldsymbol{U}_{ij} a_i^* a_j^* (a_i.a_j)$

Atom	*x*	*y*	*z*	U_{eq} (Å^2)
C1	0.3238 (7)	0.2262 (7)	0.7372 (6)	0.0429 (16)
C2	0.2139 (9)	0.1041 (7)	0.6439 (6)	0.061 (2)
C3	0.1727 (10)	-0.0360 (7)	0.6731 (7)	0.072 (2)
C4	0.2383 (10)	-0.0541 (8)	0.7915 (8)	0.078 (2)
C5	0.3481 (10)	0.0732 (9)	0.8847 (7)	0.072 (2)
C6	0.3907 (8)	0.2139 (7)	0.8565 (6)	0.0557 (19)
C7	0.3546 (7)	0.5346 (6)	0.5937 (5)	0.0330 (15)
C8	0.5008 (7)	0.6074 (6)	0.7009 (5)	0.0374 (16)
C9	0.5056 (8)	0.4986 (7)	0.7676 (5)	0.0464 (17)
C10	0.6423 (10)	0.7539 (8)	0.7463 (7)	0.074 (2)
C11	0.2790 (7)	0.5866 (6)	0.4855 (5)	0.0375 (16)
C12	0.1292 (7)	0.4830 (6)	0.3939 (5)	0.0369 (15)
C13	0.0661 (7)	0.5357 (6)	0.2947 (5)	0.0358 (15)
C14	0.1364 (7)	0.6789 (6)	0.2769 (5)	0.0382 (16)
C15	0.2817 (8)	0.7818 (6)	0.3644 (5)	0.0471 (17)
C16	0.3485 (7)	0.7313 (6)	0.4686 (5)	0.0456 (17)
C17	-0.0931 (8)	0.5496 (7)	0.1132 (6)	0.0420 (17)
C18	0.0680 (9)	0.8105 (6)	0.1003 (5)	0.061 (2)
N1	0.3698 (6)	0.3706 (6)	0.7066 (4)	0.0405 (13)
N2	0.2760 (6)	0.3923 (5)	0.5983 (4)	0.0385 (13)
N3	0.0336 (6)	0.6854 (5)	0.1647 (4)	0.0382 (13)
O1	0.6648 (6)	0.8635 (5)	0.6996 (5)	0.0969 (19)
O2	-0.0802 (5)	0.4521 (4)	0.1927 (3)	0.0453 (12)
O3	-0.2075 (5)	0.5099 (4)	0.0152 (4)	0.0537 (13)

Table 3. Selected bond distances (Å), angles (°) and torsion angles (°)

Bond distance		*Bond angles*		*Torsion angles*	
C1-N1	1.425 (7)	N1-C9-C8	108.1 (5)	C11-C7-C8-C10	-5.1 (11)
C7-N2	1.324 (7)	C14-C13-O2	108.9 (5)	C7-C8-C10-O1	4.4 (14)
C9-N1	1.346 (6)	C13-C14- N3	106.8 (5)	C6-C1-N1-C9	17.3 (9)
C10-O1	1.212 (7)	C15-C14- N3	133.5 (5)	C2-C1-N1-C9	-162.2 (6)
C13-O2	1.405 (6)	O3-C17- N3	129.1 (5)	C6-C1-N1-N2	-166.0 (5)
C14-N3	1.383 (6)	O3-C17- O2	121.6 (5)	C2-C1-N1-N2	14.5 (8)
C17-O3	1.212 (6)	N3-C17- O2	109.3 (4)	C11-C7-N2-N1	179.9 (5)
C17-N3	1.343 (6)	C9-N1-N2	110.4 (4)	O3-C17-N3-C18	-6.9 (9)
C17-O2	1.383 (6)	N2-N1-C1	120.8 (5)	C15-C14-N3-C18	6.5 (10)
C18-N3	1.451 (6)	C7-N2-N1	106.3 (4)	N2-C7-C11-C16	-179.5 (6)
N1-N2	1.377 (5)	C1-N3-C14	109.2 (4)	C8-C7-C11-C16	1.0 (10)
		C17-O2-C13	105.7 (4)	N2-C7-C11-C12	-0.1 (8)
				C8-C7-C11-C12	-179.7 (6)

C-N bond lengths range from 1.324 (7) Å to 1.451 (6) Å. C-O bond lengths range from 1.212 (6) Å to 1.405 (6) Å. N1-N2 bond length is 1.377 (5) Å. The bond lengths and angles are within expected ranges, and are similar to those that have been reported in other studies (7-10). The rings A (C1–C6), B (C7-C9/N1/N2), C (C11–C16), and D (C13/C14/N3/C17/O2) are each essentially planar. The dihedral angles between the rings A and B, B and C, and C and D are 15.8 (3), 1.5 (4) and 0.6 (4)°, respectively.

The inter and intra-molecular C–H...O interactions are provided for the evaluation for the stability of the molecular C–H...O interactions (Fig. 3, Table 4). All the H atoms were positioned geometrically and refined using a riding model approximation, with d (C—H) = 0.93 Å, and U_{iso} (H) = 1.2 U_{eq} (C). Also, the methyl H atoms were positioned geometrically, with d (C—H) = 0.96 Å and U_{iso} (H) = 1.5 U_{eq} (C). The intra and inter-molecular hydrogen bonds were calculated using PARST95 (11).

Table 4. Hydrogen bonds

D	H	A	D-H	H..A	D..A	D-H...A	Symmetry
C2	H2	N2	0.9298	2.4772	2.798 (8)	100.38	
C9	H9	O3	0.9300	2.3081	3.232 (7)	172.32	1+*x*, *y*, 1+*z*
C16	H16	O1	0.9298	2.1972	3.060 (7)	153.97	
C18	H18A	O1	0.9600	2.4182	3.349 (7)	163.31	1-*x*, 2-*y*, 1-*z*

IR and NMR analysis

The significant absorption bands in the IR spectrum of the title compound due to the aldehyde group in pyrazol ring are ν (C-H) (2720 cm^{-1}) and ν (CO) (1688 cm^{-1}). The signal corresponding to the resonance of aldehyde in the 1H NMR spectrum of the compound is observed as a singlet at 10.05 ppm. The ν (CO) frequency of the lactam carbonyl group in 2-benzoxazolinone ring is 1760 cm^{-1} and is consistent with other studies (11). These experimental results are confirmed by the X-ray study.

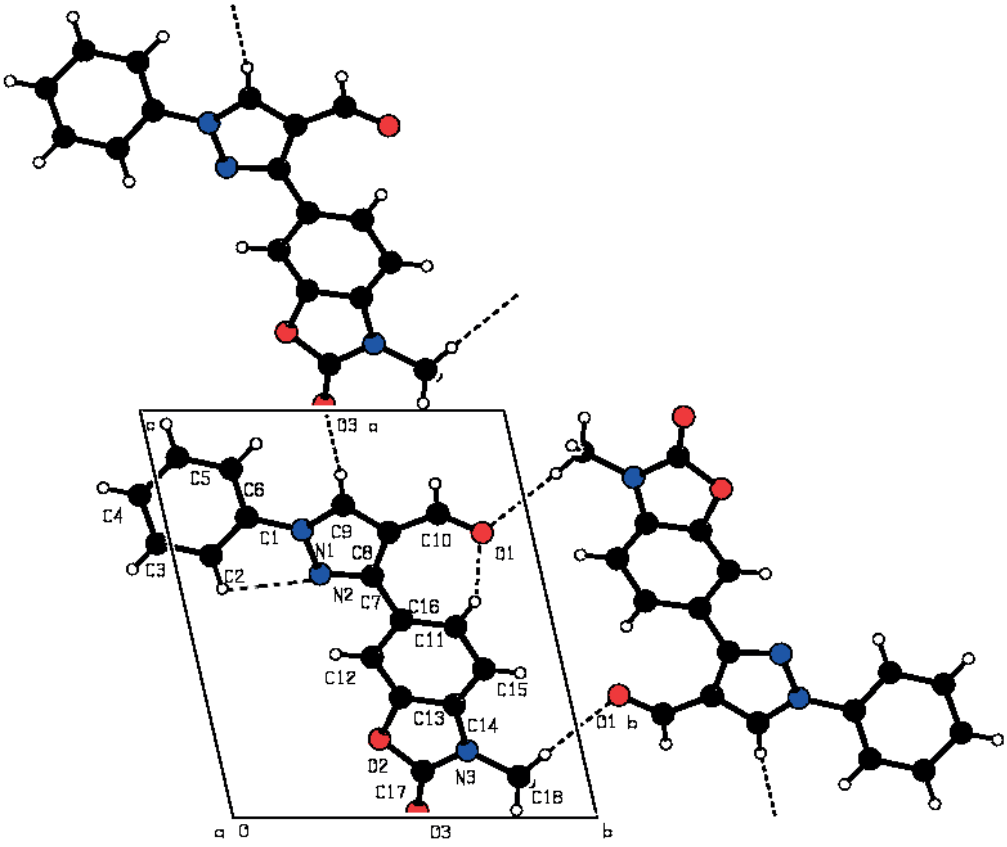

Figure 3. View of the crystal packing of the title compound, along the a-axis. Hydrogen bonds are indicated by dashed lines.

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