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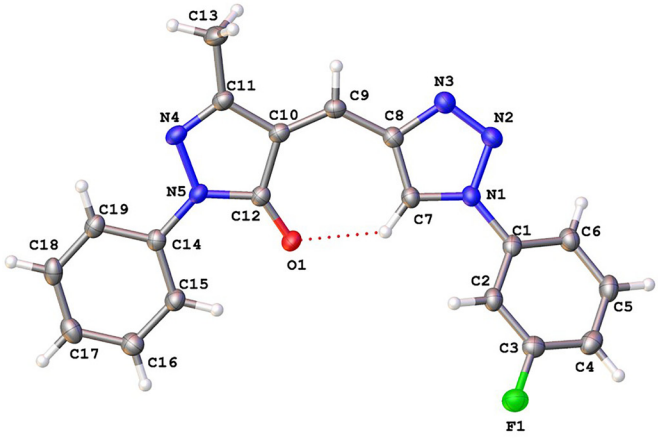
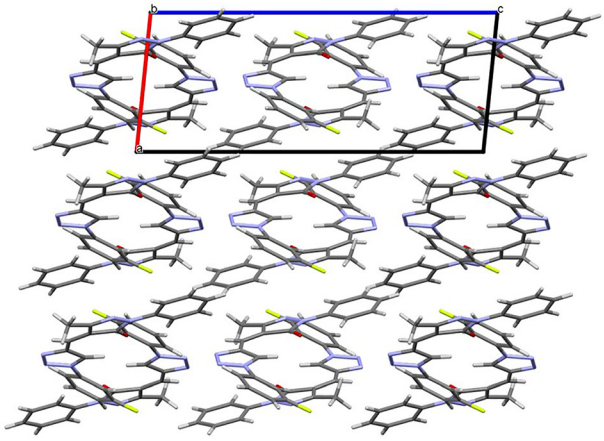
Synthesis and crystal structure of (*Z*)-4-((1-(3-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methylene)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, $C_{19}H_{14}FN_5O$





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Abstract

$C_{19}H_{14}FN_5O$, monoclinic, $P2_1/c$ (no. 14), a = 7.2944(3) Å, b = 12.2032(5) Å, c = 18.1070(7) Å, β = 95.807(4)°, V = 1603.52(11) Å^3, Z = 4, $R_{gt}(F)$ = 0.0451, wR_{ref} = 0.1217, T = 100(2) K.

CCDC no.: 2370815

Table 1: Data collection and handling.

Crystal:	Red block
Size:	0.40 × 0.20 × 0.05 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.10 mm^{-1}
Diffractometer, scan mode:	Xcalibur, ω
θ_{max}, completeness:	30.1°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	13,035, 4,123, 0.038
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 3291
$N(param)_{refined}$:	236
Programs:	Mercury,[1] CrysAlis^{PRO},[2] SHELX[3,4], OLEX2[5]

The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

1 Source of material

The starting compounds were obtained from commercial sources and were used without further purification. The NMR

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
F1	0.85831 (12)	−0.02841 (8)	0.57544 (5)	0.0344 (2)
O1	0.31559 (14)	0.37148 (8)	0.52510 (5)	0.0249 (2)
N1	0.53509 (15)	0.16778 (9)	0.37465 (6)	0.0216 (2)
N2	0.52130 (17)	0.18759 (10)	0.29966 (6)	0.0269 (3)
N3	0.45416 (16)	0.28576 (10)	0.28952 (6)	0.0264 (3)
N4	0.19083 (16)	0.64279 (9)	0.48100 (6)	0.0236 (3)
N5	0.21264 (15)	0.55153 (9)	0.52934 (6)	0.0210 (2)
C1	0.61602 (18)	0.06841 (11)	0.40465 (7)	0.0219 (3)
C2	0.70300 (18)	0.06977 (12)	0.47658 (8)	0.0237 (3)
H2	0.710435	0.134900	0.505462	0.028*
C3	0.77805 (19)	−0.02742 (12)	0.50425 (8)	0.0253 (3)
C4	0.7764 (2)	−0.12248 (13)	0.46349 (8)	0.0288 (3)
H4	0.833598	−0.187237	0.483766	0.035*
C5	0.6886 (2)	−0.12107 (12)	0.39180 (8)	0.0293 (3)
H5	0.685261	−0.185931	0.362680	0.035*
C6	0.6057 (2)	−0.02644 (12)	0.36203 (8)	0.0264 (3)
H6	0.543136	−0.026497	0.313399	0.032*
C7	0.47463 (17)	0.25396 (11)	0.41123 (7)	0.0213 (3)
H7	0.468793	0.260715	0.463209	0.026*
C8	0.42278 (18)	0.33063 (11)	0.35724 (7)	0.0221 (3)
C9	0.35652 (18)	0.44181 (11)	0.36054 (7)	0.0221 (3)
H9	0.350379	0.481257	0.315129	0.027*
C10	0.30190 (17)	0.49801 (11)	0.41889 (7)	0.0210 (3)
C11	0.24228 (18)	0.61180 (12)	0.41765 (7)	0.0231 (3)
C12	0.28140 (17)	0.46076 (11)	0.49567 (7)	0.0203 (3)
C13	0.2420 (2)	0.68947 (13)	0.35449 (8)	0.0324 (3)
H13A	0.189015	0.759535	0.368074	0.049*
H13B	0.168193	0.659015	0.311080	0.049*
H13C	0.368730	0.701107	0.342643	0.049*
C14	0.16336 (17)	0.56322 (11)	0.60260 (7)	0.0209 (3)
C15	0.19294 (19)	0.47839 (12)	0.65457 (8)	0.0253 (3)
H15	0.247680	0.411530	0.641274	0.030*
C16	0.1415 (2)	0.49292 (12)	0.72570 (8)	0.0282 (3)
H16	0.162104	0.435540	0.761020	0.034*
C17	0.0607 (2)	0.58972 (13)	0.74607 (8)	0.0294 (3)
H17	0.023420	0.598233	0.794520	0.035*
C18	0.03504 (19)	0.67396 (13)	0.69457 (8)	0.0279 (3)
H18	−0.017955	0.741056	0.708446	0.033*
C19	0.08539 (18)	0.66190 (12)	0.62328 (8)	0.0240 (3)
H19	0.067084	0.720304	0.588627	0.029*

spectra were recorded on a Varian MR400 spectrometer with standard pulse sequences operating at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR. For the NMR spectra, DMSO-d_6 was used as solvent. Chemical shift values are referenced to residual protons (δ 2.49 ppm) and carbons (δ 39.6 ppm) of the solvent as an internal standard. LC/MS spectra were recorded on a ELSD Alltech 3,300 liquid chromatograph equipped with a UV detector (λ_{max} = 254 nm), API-150EX mass spectrometer and using a Zorbax SB-C18 column, Phenomenex (100 × 4 mm) Rapid Resolution HT Cartridge 4.6 × 30 mm, 1.8-μm. Elution started with 0.1 M solution of HCOOH in water and ended with 0.1 M solution of HCOOH in acetonitrile used a linear gradient at a flow rate of 0.15 ml/min and an analysis cycle time of 25 min.

Synthesis of the title compound **4**. The mixture of 1-(3-fluorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (1 mmol, 150 mg), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (1 mmol, 136 mg), sodium acetate (0.2 mmol, 13 mg) was dissolved in ethanol (10 mL). The solution was refluxed for 2 h at 100 °C. After completion of the reaction, according to TLC data, the reaction mixture was cooled to room temperature. The precipitate was filtered off, washed with ethanol, and crystallized from ethanol, giving the yield of 260 mg, 96.3 %.

Red crystals, m.p. 242–243 °C, LC/MS $[MH]^+$ 348.2.

2 Experimental details

Using Olex2,[5] the structure was solved by with the ShelXT[4] structure solution program. Positions of the hydrogen atoms were located from electron density difference maps and refined by riding models with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl group and n = 1.2 for other hydrogen atoms).

3 Comment

3.1 Introduction

The development of new biologically active compounds containing the cores of 1,2,3-triazole and pyrazole is of undeniable interest for pharmaceutical and medical research, as many of these compounds exhibit various types of pharmacological activity.[6–12] One of the key advantages of hybrid molecules containing the cores of 1,2,3-triazole and pyrazole is the opportunity for their broad structural modification, allowing for targeted variation of the molecular structure aimed at improving the pharmacological properties of the substance. Earlier, as demonstrated by the synthesis of diethyl 2,6-dimethyl-4-(1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)1,4-dihydropyridine-3,5-dicarboxylate we have shown the possibility of synthesizing 1,2,3-triazole hybrid molecules.[13] Continuing these studies, we have developed a method for the synthesis of (*Z*)-4-((1-(3-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methylene)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one and its molecular and crystal structure has been investigated.

3.2 Synthetic background

The reaction was carried out at 100 °C for 2 h in ethanol by stirring 1-(3-fluorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde, 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, and sodium acetate. The 1-(3-fluorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde was obtained from *o*-nitroaniline according to the method described in Ref.[13] The product 4-((1-(3-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methylene)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one was crystallized from absolute ethanol with a yield of 96 %.

3.3 Database survey

Any structures with the (*Z*)-4-((1*H*-1,2,3-triazol-4-yl) methylene)-3-methyl-1*H*-pyrazol-5(4*H*)-one fragment are deposited by now with the Cambridge Structural Database (CSD).[14] The dipyrazolylmethane derivatives as the closest analogs of titled compound are rare found moiety. Only five crystal structures containing this aforementioned fragment are deposited with the CCDC.

3.4 Structural comment

The asymmetric unit of the title structure contains one complete molecule (see left part of the figure). The phenyl substituent is coplanar to the pyrazole ring (the C12–N5–C14–C15 torsion angle is −4.5(2)°) due to the formation of the C15–H15···O1 intramolecular hydrogen bond (H···O 2.26 Å, C–H···O 124°) on the one hand and, despite of the presence of the shortened intramolecular contacts H19···N4 2.42 Å (the van der Waals radii sum[15] is 2.66 Å) on the other hand. Meanwhile the triazole ring is slightly turned around C8–C9 bond (the C7–C8–C9–C10 torsion angle is −10.3(2)°). Such position is stabilized by the strong intramolecular C7–H7···O1 intramolecular hydrogen bond (H···O 2.14 Å, C–H···O 131°). The conjugation between the lone pair of the N1 atom and the fluorophenyl substituent is disrupted due to the rotation around the N(1)–C(6) bond (torsion angle C7–N1–C1–C2 −24.6(2)°), as evidenced by the elongation of the N1–C1 bond to 1.432(2) Å compared to the average value of 1.390 Å.[16] However, noticeable steric repulsion is still present in the molecule, indicated by shortened intramolecular contacts N2···H6 2.63 Å (2.66 Å), H2···C7 2.72 Å (2.87 Å) and H2···H7 2.40 Å (2.42 Å). In the crystal phase molecules of the titled compound form layers parallel to (1 0 0) crystallographic plane due to the stacking interactions between heterocycles rings (3.30 Å) (see the right part of the figure).

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

1. Macrae, C. F.; Sovago, I.; Cottrell, S. J.; Galek, P. T. A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G. P.; Stevens, J. S.; Towler, M.; Wood, P. A. Mercury 4.0: From Visualization to Analysis, Design and Prediction. *J. Appl. Crystallogr.* **2020**, *53*, 226–235.
2. Oxford Diffraction CrysAlis^{PRO} (Version 1.171.41.93a); Oxford Diffraction Ltd.: Oxford, UK, 2020.
3. Sheldrick, G. M. A Short History of SHELX. *Acta Crystallogr.* **2008**, *A64*, 112–122.
4. Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr.* **2015**, *C71*, 3–8.
5. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: A Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Cryst*. **2009**, *42*, 339–341.
6. Sharma, K.; Kumar, A.; Prakash, R.; Tripathi, A.; Singh, R.; Bajpai, R.; Sahasrabuddhe, A. A.; Singh, D.; Narender, T. Pyrazoline Analogues: Design, Synthesis, and Evaluation of Anti-osteoporosis Activity. *Bioorg. Med. Chem. Lett.* **2022**, *60*, 128585.
7. Vaishnani, M. J.; Bijani, S.; Rahamathulla, M.; Baldaniya, L.; Jain, V.; Thajudeen, K. Y.; Ahmed, M. M.; Farhana, S. A.; Pasha, I. Biological Importance and Synthesis of 1,2,3-Triazole Derivatives: A Review. *Green Chem. Lett. Rev.* **2024**, *17*, 2307989.
8. Faisal, M.; Saeed, A.; Hussain, S.; Dar, P.; Larik, F. A. Recent Developments in Synthetic Chemistry and Biological Activities of Pyrazole Derivatives. *J. Chem. Sci.* **2019**, *131*, 1–30.
9. Esvet, A.; Berber, I. Antibacterial and Antifungal Activities of New Pyrazolo [3,4*d*] Pyridazin Derivatives. *Eur. J. Med. Chem*. **2005**, *40*, 401–405.
10. Nugent, R. A.; Murphy, M.; Schlachter, S. T.; Dunn, C. J.; Smith, R. J.; Staite, N. D.; Galinet, L. A.; Shields, S. K.; Aspar, D. G.; Richard, K. A.; Rohloff, N. A. Pyrazoline Bisphosphonate Esters as Novel Antiinflammatory and Antiarthritic Agents. *J. Med. Chem.* **1993**, *36*, 134–139.

11. Antonini, I.; Polucci, P.; Magnano, A.; Martelli, S. Synthesis, Antitumor Cytotoxicity, and DNA-Binding of Novel *N*-5,2-Di(ω-aminoalkyl)-2,6-Dihydropyrazolo[3,4,5-ki]acridine-5-Carboxamides. *J. Med. Chem.* **2001**, *44* (20), 3329–3333.
12. Fletcher, J. T.; Christensen, J. A.; Villa, E. M. Tandem Synthesis of 1-Formyl-1,2,3-triazoles. *Tetrahedron Lett*. **2017**, *58*, 4450–4454.
13. Konovalova, I. S.; Geleverya, A. O.; Kovalenko, S. M.; Reiss, G. J. One-pot Synthesis and Crystal Structure of Diethyl 2,6-Dimethyl-4-(1-(2-Nitrophenyl)-1*H*-1,2,3-Triazol-4-Yl)-1,4-Dihydropyridine-3,5-Dicarboxylate, $C_{21}H_{23}N_5O_6$. *Z. Kristallogr. N. Cryst. Struct.* **2023**, *238*, 381–384.
14. Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. The Cambridge Structural Database. *Acta Crystallogr.* **2016**, *B72*, 171–179.
15. Zefirov, Y. V. Reduced Intermolecular Contacts and Specific Interactions in Molecular Crystals. *Kristallografiya* **1997**, *42*, 936–958.
16. Bürgi, H.-B.; Dunitz, J. D. *Structure Correlation*, Vol. 2; VCH: Weinheim, 1994; pp. 741–784.