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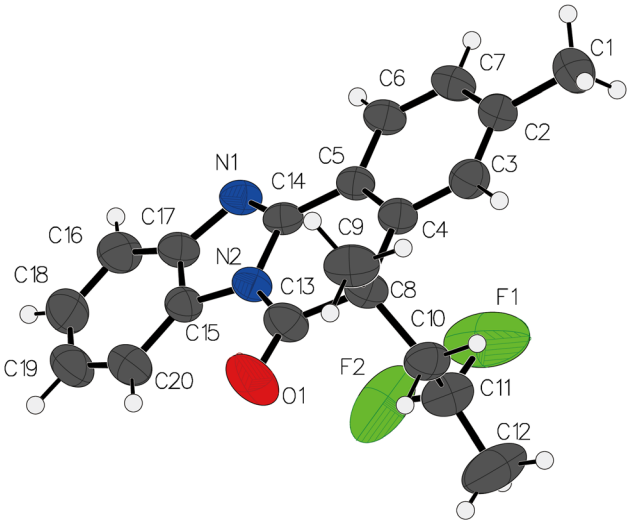
Crystal structure of 5-(2,2-difluoropropyl)-5-methylbenzo[4,5]imidazo[2,1-*a*] isoquinolin-6(5*H*)-one, $C_{20}H_{18}F_2N_2O$



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Abstract

$C_{20}H_{18}F_2N_2O$, monoclinic, $P2_1/n$ (no. 14), a = 10.7795(8) Å, b = 12.7526(7) Å, c = 13.4631(10) Å, β = 111.105(8)°, V = 1726.6(2) Å^3, Z = 4, $R_{gt}(F)$ = 0.0737 $wR_{ref}(F^2)$ = 0.1862, T = 293 K.

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Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	colourless plate
Size:	0.21 × 0.15 × 0.10 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.10 mm^{-1}
Diffractometer, scan mode:	RIGAKU, φ and ω scans
θ_{max}, completeness:	29.2°, 100 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	19689, 4225, 0.046
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 2,300
$N(param)_{refined}$:	229
Programs:	Rigaku,[1] SHELX,[2,3] Olex2[4]

1 Source of materials

The target compound was synthesized via an electrochemical method under the following typical conditions: A 20 mL test tube equipped with a stirring bar was charged with 2-methyl-1-(2-phenyl-1*H*-benzo[d]imidazol-1-yl)prop-2-en-1-one (0.2 mmol), sodium difluoromethanesulfinate ($MeCF_2SO_2Na$, 0.6 mmol), lithium perchlorate ($LiClO_4$, 0.3 M), acetonitrile (MeCN, 4.5 mL), and water (H_2O, 1.5 mL). A carbon plate (10 mm × 10 mm × 3 mm) and a platinum plate (10 mm × 10 mm × 0.2 mm) were employed as the anode and cathode, respectively. The electrolysis was performed at a constant voltage of 2.1 V at room temperature for 3 h. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (EtOAc, 10 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography.

2 Experimental details

Hydrogen atoms were positioned in geometrically idealized locations and refined using a riding model. The crystal structure was solved using ShelXT [2] and refined with ShelXL,[3] implemented within the Olex2 software suite[4].

3 Comment

Benzo[4,5]imidazo[2,1-*a*]isoquinoline derivatives have garnered significant attention in recent years due to their

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

	x	*y*	*z*	U_{iso}*/U_{eq}
F1	0.8538 (3)	0.5073 (3)	0.4103 (2)	0.1526 (13)
F2	0.6637 (3)	0.47467 (19)	0.40747 (19)	0.1385 (12)
O1	0.4223 (2)	0.59949 (18)	0.2647 (2)	0.0874 (8)
N1	0.5302 (2)	0.34805 (16)	0.07715 (16)	0.0433 (5)
N2	0.48549 (19)	0.47779 (16)	0.17250 (16)	0.0408 (5)
C1	1.0462 (3)	0.6615 (3)	0.1559 (3)	0.0680 (9)
H1A	1.122723	0.634990	0.212416	0.102*
H1B	1.034022	0.734216	0.168542	0.102*
H1C	1.059254	0.654320	0.089351	0.102*
C2	0.9243 (3)	0.6002 (2)	0.1518 (2)	0.0478 (7)
C3	0.8402 (3)	0.6374 (2)	0.2007 (2)	0.0480 (7)
H3	0.862013	0.699483	0.239444	0.058*
C4	0.7240 (2)	0.58549 (19)	0.1941 (2)	0.0415 (6)
C5	0.6921 (2)	0.49260 (18)	0.13524 (19)	0.0371 (6)
C6	0.7771 (2)	0.4543 (2)	0.0862 (2)	0.0431 (6)
H6	0.756346	0.392336	0.047263	0.052*
C7	0.8905 (3)	0.5074 (2)	0.0951 (2)	0.0489 (7)
H7	0.946381	0.480617	0.062293	0.059*
C8	0.6322 (3)	0.6320 (2)	0.2466 (2)	0.0447 (6)
C9	0.5858 (3)	0.7412 (2)	0.1969 (3)	0.0626 (9)
H9A	0.661671	0.785936	0.210115	0.094*
H9B	0.526910	0.771410	0.228155	0.094*
H9C	0.539999	0.733898	0.121472	0.094*
C10	0.7026 (3)	0.6475 (2)	0.3680 (2)	0.0537 (7)
H10A	0.777002	0.694756	0.379163	0.064*
H10B	0.640900	0.682559	0.394507	0.064*
C11	0.7540 (4)	0.5517 (3)	0.4351 (3)	0.0701 (9)
C12	0.8018 (5)	0.5663 (4)	0.5514 (3)	0.1075 (15)
H12A	0.730731	0.592566	0.571384	0.161*
H12B	0.874097	0.615470	0.572469	0.161*
H12C	0.831870	0.500290	0.585997	0.161*
C13	0.5054 (3)	0.5700 (2)	0.2303 (2)	0.0515 (7)
C14	0.5721 (2)	0.43685 (18)	0.12580 (19)	0.0370 (6)
C15	0.3805 (2)	0.40557 (19)	0.15053 (19)	0.0412 (6)
C16	0.4097 (3)	0.3267 (2)	0.0917 (2)	0.0439 (6)
C17	0.3253 (3)	0.2417 (2)	0.0561 (2)	0.0565 (8)
H17	0.342928	0.189312	0.015026	0.068*
C18	0.2141 (3)	0.2377 (3)	0.0840 (3)	0.0625 (8)
H18	0.156308	0.180970	0.062184	0.075*
C19	0.1871 (3)	0.3167 (3)	0.1439 (3)	0.0631 (9)
H19	0.111314	0.311455	0.161304	0.076*
C20	0.2686 (3)	0.4029 (2)	0.1787 (2)	0.0544 (7)
H20	0.249782	0.455933	0.218544	0.065*

diverse biological activities and potential applications in medicinal chemistry.[5–11] The present study focuses on the synthesis and structural elucidation of 5-(2,2-difluoropropyl) -5-methylbenzo[4,5]imidazo[2,1-*a*]isoquinolin-6(5H)-one.

The central benzo[4,5]imidazo[2,1-a]isoquinoline core exhibits a nearly planar conformation, with the maximum deviation from the mean plane being observed at C8 by 0.93 Å. This planarity is consistent with the conjugated aromatic system, facilitating π-π stacking interactions in the crystal.[12–17] The substituents at the 5-position include a 2,2-difluoropropyl group and a methyl group. The difluoropropyl group adopts an extended conformation, with the C–C–F bond angles ranging from 108.0° to 110.9°, while the C–F bond lengths are measured as 1.338(5) Å and 1.359(6) Å. The presence of the two electronegative fluorine atoms introduces notable steric and electronic effects, which influence the overall molecular packing.

The molecular packing is stabilized by a combination of π-π stacking and weak intermolecular interactions. Significant π-π stacking occurs between adjacent aromatic rings, with a centroid-to-centroid distance of 3.2 Å. Additionally, weak C–H···F interactions are observed, contributing to the stability of the three-dimensional crystal lattice.

In summary, the structural elucidation of 5-(2,2-difluoropropyl)-5-methylbenzo [4,5]imidazo[2,1-a]isoquinolin-6(5H)-one highlights the planar aromatic framework, the spatial arrangement of the fluorinated propyl group, and the key intermolecular interactions that govern its crystal packing.

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References

1. Rigaku, O. D. *CrysAlisPRO*; Rigaku Oxford Diffraction Ltd: Yarnton, Oxfordshire, England, 2017.
2. Sheldrick, G. M. Shelxt–Integrated Space-Group and Crystal-Structure Determination. *Acta Crystallogr. Sect. A: Found. Adv.* **2015**, *71*, 3–8.
3. Sheldrick, G. M. Crystal Structure Refinement with Shelxl. *Acta Crystallogr. Sect. C: Struct. Chem.* **2015**, *71*, 3–8.
4. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A.; Puschmann, H. Olex2: a Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Crystallogr.* **2009**, *42*, 339–341.
5. Kraus, G. A.; Gupta, V.; Kohut, M.; Singh, N. A Direct Synthesis of 5, 6-Dihydroindolo[2,1-*a*]isoquinolines that Exhibit Immunosuppressive Activity. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5539–5542.
6. Low, J. N.; Insuasty, B.; Torres, H.; Cobo, J. 6-(4–Fluorophenyl)-5, 6-dihydrobenzimidazo[1,2-*c*]quinazoline. *Acta Crystallogr. Sect. E* **2003**, *59*, o1801–o1803.

7. Nandi, S.; Samanta, S.; Jana, S.; Ray, J. K. Synthesis of Substituted Benzimidazo[2,1-*a*]isoquinolines and its Condensed Analogues Using Pd(0)-catalyzed cyclization/C–H Activation. *Tetrahedron Lett.* **2010**, *51*, 5294–5297.
8. Ooyama, Y.; Nakamura, T.; Yoshida, K. Heterocyclic Quinol-type Fluorophores. Synthesis of Novel Imidazoanthraquinol Derivatives and Their Photophysical Properties in Benzene and in the Crystalline State. *New J. Chem.* **2005**, *29*, 447–456.
9. Özbey, S.; Kaynak, F. B.; Göker, H.; Kuş, C. Synthesis and Crystal Structure Elucidation of 1-(4-Fluorobenzyl)-2-(4-cyanophenyl)-1h-Benzimidazole-5-Carbonitrile. *J. Chem. Crystallogr.* **2004**, *34*, 851–858.
10. Yang, X.; Jones, R. A.; Lai, R. J.; Waheed, A.; Oye, M. M.; Holmes, A. L. Supramolecular Assembly of Nanometer-Sized Heterobimetallic 3d-4f Complexes Formed with Benzimidazole Based N,O-donor Ligands. *Polyhedron* **2006**, *25*, 881–887.
11. Zheng, L.; Hua, R. Modular Assembly of Ring–Fused and π–Extended Phenanthroimidazoles *via* C–H Activation and Alkyne Annulation. *J.Org. Chem.* **2014**, *79*, 3930–3936.
12. Bian, Z. –Q.; Wang, K. –Z.; Jin, L. –P. Syntheses, Spectroscopic and Crystal Structural Studies of Novel Imidazo[4,5-*f*]1,10-phenanthroline Derivatives and their Eu(III) Ternary Complexes with Dibenzoylmethane. *Polyhedron* **2002**, *21*, 313–319.
13. Chang, M. –Y.; Wu, M. –H.; Chen, Y. –L. Synthesis of Dihydrobenzoimidazo [2,1-*a*]isoquinolines. *Tetrahedron Lett.* **2012**, *53*, 4156–4160.
14. Dinnebier, R. E.; Sieger, P.; Nar, H.; Shankland, K.; David, W. I. F. Structural Characterization of Three Crystalline Modifications of Telmisartan by Single Crystal and High–Resolution X–Ray Powder Diffraction. *J. Pharm. Sci.* **2000**, *89*, 1465–1479.
15. Gilbert J. G.; Addison A. W.; Prabakaran P.; Butcher R. J.; Bocelli G. A Novel Paradigm for Metal-induced Ring Flipping in the Copper(II) Complex of 1,2-bis(*N*-methylbenzimidazol-2′-yl)benzene Triflate. *Inorg. Chem. Commun.* **2004**, *7*, 701–704.
16. Kazak C.; Yilmaz V. T.; Goker H.; Kus C. 1-*n*–Butyl-2-(4′-fluorophenyl) -1*H*-benzimidazole-6-carbonitrile. *Acta Crystallogr. Sect. E* **2004**, *60*, m819–m821.
17. Ramesh, D.; Gangadhar, M.; Babu Nanubolu, J.; Adiyala, P.-R. Visible-light-induced Deaminative Alkylation/Cyclization of Alkyl Amines with *N*-Methacryloyl-2-phenylbenzoimidazoles in Continuous-Flow Organo-Photocatalysis. *Đ. Org. Chem*. **2021**, *86*, 12908–12921.