Crystal structure of 6-(4-difluoromethoxy-3-methoxyphenyl)-3(2H)-pyridazinone, C₁₂H₁₀F₂N₂O₃

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Abstract

C₁₂H₁₀F₂N₂O₃, monoclinic, *P*12₁/n1 (no. 14), *a* = 7.239(1) Å, *b* = 15.838(1) Å, *c* = 10.099(1) Å, β = 91.991(6)°, *V* = 1157.2 Å³, *Z* = 4, *R*_{gt}(*F*) = 0.033, *wR*_{ref}(*F*²) = 0.093, *T* = 109 K.

Source of material

Zardaverine was purchased from SIGMA and crystallized by slow evaporation in methanol at room temperature.

Discussion

6-(4-difluoromethoxy-3-methoxyphenyl)-3(2H)-pyridazinone (zardaverine) selectively inhibits phosphodiesterase (PDE) isozymes III and IV [1], which regulate cyclic nucleotide levels in eukaryotic cells. The title compound, along with other dialkoxyphenol-containing compounds, have been examined as possible treatments for acute respiratory failure [1–3]. Zardaverine has also been used as a template compound to computationally generate a library of PDE4 inhibitors [4]. Two protein structures of zardaverine complexed with PDE4 type D have been reported. One structure was solved to a resolution of 2.9 Å [5] and the other was solved to 1.54 Å [6]. In the higher resolution structure of PDE4D–zardaverine, the compound is found in three different conformations: A, B, and C, with occupancies of 47 %, 33 %, and 20 %, respectively. In all three conformers, the two rings are not co-planar. The torsion angles along C6–C1–C7–N2 are 39.6° for A, –146.6° for B, and –165.1° for C. The A and B conformers are essentially equivalent except that the pyridazinone ring is flipped along the C1–C7 bond. This is possible because the pyridazinone ring is not anchored by H bonds to the protein.

In contrast, in the crystal structure reported here, the N1–H1···O3(–*x*, –*y* + 1, –*z* + 1) H-bond stabilizes the pyridazinone ring in a single conformation, and the crystal packing ensures that the two rings of the compound are essentially co-planar, with a C6–C1–C7–N2 torsion angle of 4.9(2)°. In the reported structure,

dimers of zardaverine are observed. The H1 atom (which is the only hydrogen in the structure capable of strong hydrogen bonding) forms a H bond with O3(–*x*, –*y* + 1, –*z* + 1) of a symmetry-related molecule. This hydrogen bond is nearly ideal with an H1···O3 distance of 1.887 Å and an N1–H1···O3 angle of 174.04°. The N1–H1···O3 H-bonds are responsible for dimer formation. The molecules are packed in nearly planar layers. The O3 atom is also involved in a short contact interaction with hydrogen atom H12(–*x* + 1, –*y* + 1, –*z* + 1), where the O3···H12 distance is 2.23(1) Å, and the O3···H12–C12(–*x* + 1, –*y* + 1, –*z* + 1) angle is 163(1)°.

Table 1. Data collection and handling.

Crystal:	colorless plate, size 0.09 × 0.19 × 0.51 mm
Wavelength:	Cu K α radiation (1.54179 Å)
μ :	11.55 cm ^{–1}
Diffractometer, scan mode:	Rigaku R-Axis RAPID, ω (κ offset)
2 θ _{max} :	144.64°
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} :	41088, 2228
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 3 σ (<i>I</i> _{obs}), 2027
<i>N</i> (<i>param</i>) _{refined} :	213
Programs:	SHELXS-97 [7], HKL-2000 [8], SHELXL-97 [9], ORTEP-III [10], ORTEP-3 [11]

Table 2. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(2)	4e	0.216(2)	0.4578(9)	0.617(1)	0.036(4)
H(12)	4e	0.246(2)	0.6737(9)	0.920(1)	0.030(3)
H(8)	4e	0.293(2)	0.3838(8)	0.453(1)	0.033(3)
H(9)	4e	0.401(2)	0.3170(9)	0.265(1)	0.036(4)
H(11A)	4e	0.232(2)	0.4199(9)	0.844(1)	0.039(4)
H(6)	4e	0.233(2)	0.6709(9)	0.391(1)	0.033(3)
H(1)	4e	0.432(2)	0.541(1)	0.094(2)	0.047(4)
H(11B)	4e	0.016(2)	0.4099(9)	0.788(1)	0.036(4)
H(5)	4e	0.113(2)	0.749(1)	0.571(2)	0.040(4)
H(11C)	4e	0.066(2)	0.4270(9)	0.939(2)	0.039(4)

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Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
F(1)	4e	0.0576(1)	0.73471(5)	1.00656(7)	0.0499(5)	0.0377(4)	0.0321(4)	0.0022(3)	0.0099(3)	-0.0072(3)
O(3)	4e	0.4838(1)	0.39220(5)	0.04644(8)	0.0359(5)	0.0291(4)	0.0255(4)	0.0026(3)	0.0046(3)	0.0006(3)
O(1)	4e	0.0261(1)	0.69371(5)	0.80161(8)	0.0303(5)	0.0331(4)	0.0335(4)	0.0027(3)	0.0026(3)	-0.0090(3)
F(2)	4e	0.2375(1)	0.78922(5)	0.86334(8)	0.0594(6)	0.0403(4)	0.0458(5)	-0.0181(4)	0.0119(4)	-0.0108(3)
C(10)	4e	0.4270(2)	0.42321(7)	0.1515(1)	0.0263(6)	0.0269(5)	0.0251(5)	0.0005(4)	-0.0004(4)	0.0003(4)
N(1)	4e	0.4039(1)	0.50838(6)	0.16300(9)	0.0328(6)	0.0263(5)	0.0242(5)	0.0013(4)	0.0045(4)	0.0019(4)
C(6)	4e	0.2044(2)	0.64256(7)	0.4752(1)	0.0321(7)	0.0265(5)	0.0277(5)	-0.0020(4)	-0.0003(5)	0.0012(4)
C(5)	4e	0.1380(2)	0.68855(7)	0.5803(1)	0.0317(7)	0.0257(5)	0.0341(6)	0.0005(4)	-0.0009(5)	-0.0014(4)
C(9)	4e	0.3826(2)	0.37616(7)	0.2677(1)	0.0304(6)	0.0246(5)	0.0279(6)	-0.0006(4)	0.0014(4)	0.0017(4)
O(2)	4e	0.0896(1)	0.52886(5)	0.83307(7)	0.0425(5)	0.0293(4)	0.0266(4)	-0.0019(3)	0.0081(3)	-0.0010(3)
C(1)	4e	0.2358(2)	0.55583(7)	0.4879(1)	0.0233(6)	0.0267(5)	0.0258(5)	-0.0020(4)	-0.0016(4)	-0.0013(4)
C(2)	4e	0.1988(2)	0.51574(7)	0.6075(1)	0.0270(6)	0.0240(5)	0.0273(5)	-0.0018(4)	0.0007(4)	-0.0008(4)
N(2)	4e	0.3454(1)	0.55121(6)	0.26887(9)	0.0301(6)	0.0270(5)	0.0250(5)	0.0006(4)	0.0022(4)	0.0003(3)
C(8)	4e	0.3239(2)	0.41713(7)	0.3756(1)	0.0306(6)	0.0267(5)	0.0246(5)	-0.0016(4)	0.0012(4)	0.0016(4)
C(3)	4e	0.1318(2)	0.56142(7)	0.7131(1)	0.0250(6)	0.0287(5)	0.0263(5)	-0.0021(4)	0.0010(4)	-0.0006(4)
C(7)	4e	0.3047(2)	0.50708(7)	0.3739(1)	0.0229(6)	0.0268(5)	0.0246(5)	-0.0017(4)	-0.0011(4)	0.0008(4)
C(4)	4e	0.1025(2)	0.64826(7)	0.6975(1)	0.0256(6)	0.0290(5)	0.0301(6)	0.0000(4)	0.0017(4)	-0.0062(4)
C(12)	4e	0.1526(2)	0.71621(7)	0.8979(1)	0.0374(7)	0.0279(6)	0.0295(6)	0.0017(5)	0.0035(5)	-0.0054(4)
C(11)	4e	0.1044(2)	0.43886(7)	0.8503(1)	0.0376(8)	0.0300(6)	0.0283(6)	-0.0018(5)	0.0029(5)	0.0025(4)

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