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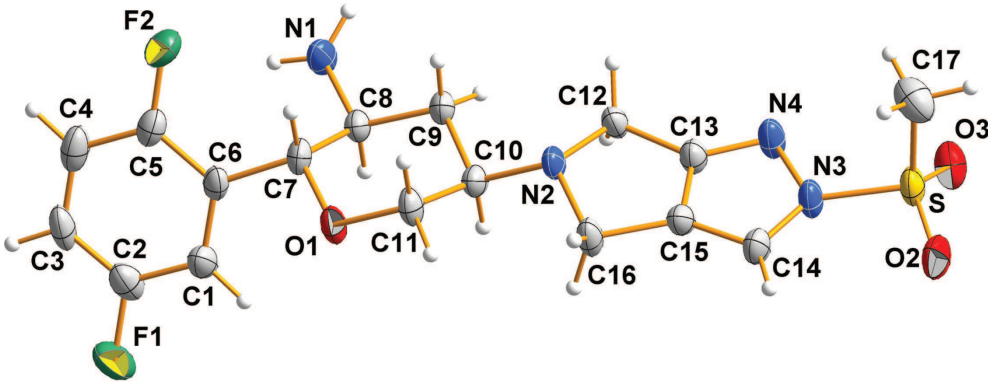
This molecule targets at type 2 diabetes - a single crystal study on (2*R*,3*S*,5*R*)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl] tetrahydro-2*H*-pyran-3-amine (Omarigliptin), $C_{17}H_{20}F_2N_4O_3S$



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Abstract

$C_{17}H_{20}F_2N_4O_3S$, triclinic, $P1$ (no. 1), $a = 6.0020(12)$ Å, $b = 6.7650(14)$ Å, $c = 11.831(2)$ Å, $\alpha = 89.39(3)°$, $\beta = 86.29(3)°$, $\gamma = 66.50(3)°$, $V = 439.55(15)$ Å^3, $Z = 1$, $R_{gt}(F) = 0.0543$, $wR_{ref}(F^2) = 0.1568$, $T = 293(2)$ K.

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Tables 1–3 contain details of the methods used and a list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colorless, block, size 0.10×0.20×0.30 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	2.32 cm^{-1}
Diffractometer, scan mode:	Nonius CAD4, $\omega/2\theta$
$2\theta_{max}$:	50.74°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	1784, 1784
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 1595
$N(param)_{refined}$:	244
Programs:	CAD4 programs [3, 4], Abbsortion correction [5], SHELX [6]

Source of material

The title compound was prepared by a literature method [1]. 16.5 g (50.4 mmol) of *tert*-butyl [(2*R*,3*S*)-5-oxo-2-(2,5-difluorophenyl)tetrahydro-2*H*-pyran-3-yl]carbamate, 19.6 g (56.8 mmol) of pyrazole salt (benzenesulfonic acid and 2-(methylsulfonyl)-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole) and 250 mL of dimethylacetamide were mixed while stirring. The resulting homogeneous solution was cooler to 268 K and 14 g (66 mmol) of sodium triacetoxyborohydride was added

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

Atom	Site	*x*	*y*	*z*	U_{iso}
H(1A)	1*a*	0.9931	0.9626	−0.0311	0.051
H(1B)	1*a*	0.8441	1.0953	−0.1217	0.051
H(1C)	1*a*	0.1147	1.2489	−0.1368	0.048
H(3B)	1*a*	0.2019	1.6789	−0.3515	0.056
H(14A)	1*a*	0.1881	0.3810	0.4725	0.044
H(4B)	1*a*	0.4931	1.7073	−0.2401	0.056
H(7A)	1*a*	0.4892	1.2994	0.0716	0.038
H(8A)	1*a*	0.5837	0.9268	−0.0624	0.036
H(9A)	1*a*	0.8087	0.7232	0.0816	0.038
H(9B)	1*a*	0.7552	0.9321	0.1540	0.038
H(10A)	1*a*	0.3998	0.7795	0.0984	0.036
H(11A)	1*a*	0.1177	1.0778	0.2023	0.042
H(11B)	1*a*	0.3235	1.1576	0.2248	0.042
H(12A)	1*a*	0.8574	0.5464	0.2769	0.041
H(12B)	1*a*	0.7464	0.4679	0.1774	0.041
H(16A)	1*a*	0.1750	0.7041	0.2471	0.048
H(16B)	1*a*	0.1791	0.8265	0.3598	0.048
H(17A)	1*a*	0.8027	−0.0265	0.6981	0.089
H(17B)	1*a*	0.6374	0.2121	0.6695	0.089
H(17C)	1*a*	0.8942	0.0965	0.6056	0.089

portionwise. The mixture was stirred for 2 h and quenched by the slow addition of a mixture of NH_4OH (17 mL) and water (35 mL). The slurry was heated to 323 K and then cooled to 295 K and filtered. The wet cake was washed with 5:1 dimethylacetamide/water (135 mL) and then water (130 mL) and dried under vacuum/N_2 sweep to afford (22 g, 96%) of the title compound as a white solid. The primary product 22 g (42 mmol) 65 mL of dimethylacetamide, and 85 mL of water were mixed, than 25 mL of H_2SO_4 in 45 mL of water were added and stirred for 20 h at room temperature. NH_4OH was added until the pH was 10.2. The slurry was filtered and washed with water (2×30 mL) and dried under vacuum/N_2 to give the title compound (14.1 g, 92%). Crystallization from ethyl acetate gave a product with greater than 99% purity. Prism-shaped crystals were obstained by slow evaporation of an ethyl acetate solution at room temperature for about 20 d.

Experimental details

The hydrogen atoms were placed on calculated positions (SHELX: AFIX 13, 23, 33, 43 and 93 option) [6].

Table 3: Fractional coordinates and atomic displacement parameters (Å^2).

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	1*a*	0.6234(2)	−0.0161(2)	0.5349(1)	0.0432(9)	0.0330(8)	0.0380(8)	−0.0121(7)	−0.0014(7)	0.0166(6)
O(1)	1*a*	0.2259(7)	1.1988(6)	0.0659(3)	0.036(2)	0.034(2)	0.033(2)	−0.008(2)	−0.001(2)	0.015(2)
F(1)	1*a*	−0.0338(9)	1.4463(8)	−0.3177(4)	0.058(3)	0.103(4)	0.055(3)	−0.037(3)	−0.027(2)	0.037(3)
N(1)	1*a*	0.855(1)	1.0226(9)	−0.0607(5)	0.033(3)	0.051(3)	0.043(3)	−0.017(3)	0.000(2)	0.021(3)
C(1)	1*a*	0.192(1)	1.340(1)	−0.1559(5)	0.035(3)	0.046(3)	0.041(3)	−0.019(3)	−0.006(3)	0.017(3)
F(2)	1*a*	0.6462(7)	1.5111(6)	−0.0587(3)	0.055(2)	0.042(2)	0.051(2)	−0.030(2)	−0.001(2)	−0.002(2)
O(2)	1*a*	0.398(1)	−0.0143(9)	0.5767(5)	0.062(4)	0.063(3)	0.065(3)	−0.032(3)	−0.008(3)	0.039(3)
N(2)	1*a*	0.4984(9)	0.7395(7)	0.2593(4)	0.034(3)	0.031(2)	0.028(2)	−0.012(2)	−0.004(2)	0.013(2)
C(2)	1*a*	0.140(1)	1.461(1)	−0.2533(5)	0.032(3)	0.051(4)	0.037(3)	−0.008(3)	−0.001(3)	0.012(3)
N(3)	1*a*	0.551(1)	0.1840(8)	0.4401(5)	0.036(3)	0.031(3)	0.037(3)	−0.008(2)	0.001(2)	0.015(2)
O(3)	1*a*	0.801(1)	−0.2031(7)	0.4835(4)	0.064(3)	0.038(2)	0.048(3)	−0.014(2)	−0.004(2)	0.011(2)
C(3)	1*a*	0.245(1)	1.599(1)	−0.2861(6)	0.045(4)	0.039(3)	0.043(3)	−0.004(3)	0.001(3)	0.022(3)
C(14)	1*a*	0.337(1)	0.360(1)	0.4354(5)	0.040(4)	0.039(3)	0.034(3)	−0.018(3)	−0.002(3)	0.013(3)
C(4)	1*a*	0.416(2)	1.616(1)	−0.2198(6)	0.061(4)	0.025(3)	0.048(4)	−0.014(3)	0.014(4)	0.011(3)
C(5)	1*a*	0.472(1)	1.4953(9)	−0.1215(5)	0.042(4)	0.027(3)	0.039(3)	−0.014(3)	0.005(3)	0.003(2)
C(6)	1*a*	0.361(1)	1.3578(8)	−0.0875(5)	0.027(3)	0.023(3)	0.035(3)	−0.005(2)	0.003(2)	0.007(2)
C(7)	1*a*	0.435(1)	1.2218(9)	0.0175(5)	0.039(4)	0.026(3)	0.031(3)	−0.014(3)	−0.001(3)	0.008(2)
C(8)	1*a*	0.641(1)	1.0010(9)	−0.0077(5)	0.033(3)	0.030(3)	0.027(3)	−0.014(3)	−0.004(2)	0.007(2)
C(9)	1*a*	0.689(1)	0.8676(9)	0.0996(5)	0.035(3)	0.028(3)	0.033(3)	−0.013(3)	−0.005(3)	0.011(2)
C(10)	1*a*	0.459(1)	0.8549(9)	0.1515(5)	0.033(3)	0.033(3)	0.025(3)	−0.015(3)	−0.003(2)	0.008(2)
C(11)	1*a*	0.269(1)	1.0827(9)	0.1707(5)	0.042(3)	0.032(3)	0.028(3)	−0.011(3)	0.000(3)	0.011(2)
C(12)	1*a*	0.713(1)	0.531(1)	0.2532(5)	0.028(3)	0.036(3)	0.037(3)	−0.010(3)	−0.007(3)	0.016(2)
C(13)	1*a*	0.630(1)	0.4010(9)	0.3350(5)	0.033(3)	0.031(3)	0.032(3)	−0.011(3)	−0.001(3)	0.009(2)
N(4)	1*a*	0.745(1)	0.2078(8)	0.3785(4)	0.034(3)	0.036(3)	0.042(3)	−0.006(2)	0.005(2)	0.016(2)
C(15)	1*a*	0.389(1)	0.498(1)	0.3653(5)	0.031(3)	0.038(3)	0.031(3)	−0.016(3)	−0.005(2)	0.011(2)
C(16)	1*a*	0.276(1)	0.711(1)	0.3066(6)	0.034(3)	0.038(3)	0.043(3)	−0.009(3)	0.000(3)	0.020(3)
C(17)	1*a*	0.754(2)	0.077(1)	0.6387(7)	0.064(5)	0.053(4)	0.053(4)	−0.012(4)	−0.018(4)	0.003(3)

The Flack-parameter refines to a value near zero, which verifys the absolute configuration of the title molecule (see the figure).

Discussion

Experimental, clinical, and epidemiological studies have shown that type 2 diabetes mellitus is a growing epidemic affecting approximately 220 million people worldwide [1, 2]. Commercial proof of concept for DPP-4 inhibitors has been established with sitagliptin, Merck's lead DPP-4 inhibitor; Omarigliptin, which was the first DPP-4 inhibitor, approved by the FDA in October 2006. Omarigliptin (MK-3102) prolong the circulating half-life of glucagonlike peptide 1 (GLP-1) and glucose-dependant insulinotropic polypeptide (GIP), incretin hormones that stimulate insulin secretion in a glucose-dependent manner. Additionally, GLP-1 has been shown to inhibit glucagon release, decrease gastric emptying, and promote the regeneration and differentiation of islet b-cells. By increasing the circulating concentration GLP-1 and GIP, DPP-4 inhibitors improve glucose control in patients with type 2 diabetes.

The molecular structure of the title compound (drug name: Omarigliptin) is shown in the Figure. All bond lengths and angles are within normal ranges. The title molecule consists of four rings, A(C1—C2—C3—C4—C5—C6), B(C7—C8—C9—C10—C11—O1), C(C12—C13—C15—C16—N2) and D(C13—C15—C14—N3—N4). The dihedral angle between C and D is 2.3(3)°. The six-members ring B is in the typical chair conformation. In the molecular structure of the title compound, there are three chiral carbon atoms, C7, C8 and C10. The configuration of the chiral carbon atoms can be obtained directly from the crystal structure: C7, C8 and C10 are *R*, *S*, and *R*, respectively. In the crystal there are no classical intermolecular hydrogen bonds. Surprisingly, the F2 atom is close to one of the hydrogen atoms of the NH_2 group as well as to the adjacent CH group. Thus a very weak bifurcated intramolecular N—H··· F and a C—H···F hydrogen bond seem to be very effective in the stabilization of the crystal structure. In the crystal structure, there are no π-π stacking interactions, as the centroid to centroid distance between the two nearest furan rings is larger than 5 Å.

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