Crystal structure of 2-(4-allyl-4-methyl-2-oxo-1,4-dihydro-2*H*-benzo[*d*]-[1,3]oxazin-6-yl)-5-cyano-pyrrole-1-carboxylic acid *tert*-butyl ester, $C_{22}H_{23}N_3O_4$

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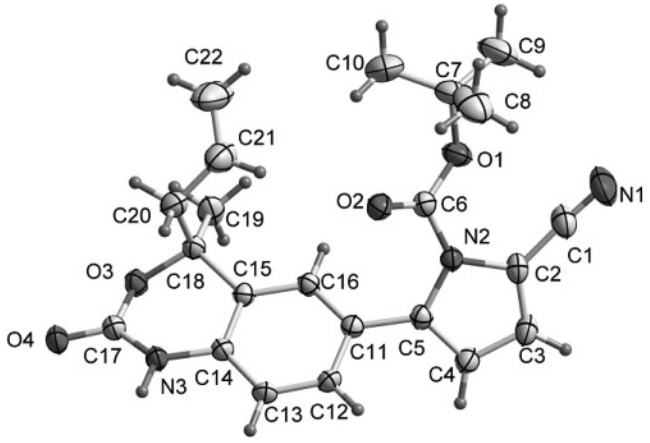

Abstract

$C_{22}H_{23}N_3O_4$, triclinic, $P\bar{1}$ (no. 2), a = 6.992(3) Å, b = 8.159(4) Å, c = 18.778(8) Å, α = 92.118(7)°, β = 93.463(7)°, γ = 101.623(7)°, V = 1045.9 Å^3, Z = 2, $R_{gt}(F)$ = 0.0576, $wR_{ref}(F^2)$ = 0.1778, T = 296 K.

Table 1. Data collection and handling.

Crystal:	colourless prisms, size 0.10×0.11×0.19 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.87 cm^{-1}
Diffractometer, scan mode:	Bruker APEX-II CCD, φ and ω
$2\theta_{max}$:	50.02°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	5363, 3640
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 2732
$N(param)_{refined}$:	242
Programs:	SHELX [10]

Source of material

The title compound, 2-(4-allyl-4-methyl-2-oxo-1,4-dihydro-2*H*-benzo[*d*][1,3]oxazin-6-yl)-5-cyano-pyrrole-1-carboxylic acid *tert*-butyl ester, was prepared following a reported procedure [9]. Starting from the raw material 1-(2-amino-5-bromophenyl)ethanone (990 mg, 4.625 mmol), the title compound was synthesized from the multi-step reactions of Grignard reaction, cyclization, Suzuki cross coupling reaction and substituted reaction, respectively. The crude product was purified by recrystallization from ethyl acetate (478 mg, yield 34%). Single crystals were grown by slow evaporation of an EtOAc/hexane (*v*/*v* 1:3) solution for several days at room temperature and colourless prismatic crystals were collected.

Experimental details

All non-hydrogen atoms were refined anisotropically. H atoms bonded to C atoms were positioned geometrically (d($C_{aromatic}$–H) = 0.93 Å, d($C_{methylene}$–H) = 0.97 Å and d(C_{methyl}–H) = 0.96 Å) and refined using a riding model, with U_{iso}(H) = 1.2 U_{eq}(C).

Discussion

2-(4-allyl-4-methyl-2-oxo-1,4-dihydro-2*H*-benzo[*d*]-[1,3]oxazin-6-yl)-5-cyano-pyrrole-1-carboxylic acid *tert*-butyl ester is a nonsteroidal progestin agonist having an in vitro potency equivalent to that of the best steroidal progestins but superior in selectivity with respect to the other members of the steroid receptor family [1-4]. When appropriately radiolabeled with a positron-emitting radionuclide, it might be useful for positron emission tomography (PET) imaging of progesterone receptor positive breast tumors. The synthesis of title compound is relatively simple, it was worth to note that a little excessive chlorosulfonyl isocyanate could improve yield and shorten the reaction time. According to the reported structure-function relationship, the pyrrole nitrogen in the molecule can be either unsubstituted or substituted with small groups, such as a methyl group. The geminal two methyl groups on the benzoxazin-2-thione ring can also be replaced by larger groups; even substitution with a 2-thienyl group gives a high affinity compound. The title compound is an important intermediate for the preparation of potential fluorine-substituted derivatives. The crystal structure of the title compound is built up of molecules containing a 5-cyanopyrrole and a benzoxazin-2-thione ring. The phenyl ring (C11-C16) and N3, C18 attached at C14, C15 are nearly coplanar. The ester group (O4–C17–O3) forms dihedral angles of 16.27(12)° with the benzene ring and the ester group (O2–C6–O1) forms dihedral angles of 31.29(12)° with the 5-cyano-pyrrole ring, respectively. The 5-cyanopyrrole and the benzoxazin-2-thione ring forms dihedral angles of 41.88(12)°. The bond lengths within the phenyl rings are between 1.382(3) Å and 1.396(3) Å. The bond lengths and angles are in good agreement with those observed in similar compounds [9]. In the crystal structure, two adjacent molecules are pairwise linked through two N–H···O hydrogen bonds forming dimers.

Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{iso}
H(3)	2*i*	0.6914	0.0015	0.1543	0.072
H(4)	2*i*	0.4615	0.1084	0.0706	0.064
H(8A)	2*i*	0.1560	–0.0133	0.4702	0.170

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Table 2. continued.

Atom	Site	x	y	z	U_{iso}
H(8B)	2*i*	0.2711	–0.0624	0.4063	0.170
H(8C)	2*i*	0.0690	–0.0105	0.3914	0.170
H(9A)	2*i*	0.5404	0.3497	0.4632	0.182
H(9B)	2*i*	0.5631	0.1625	0.4573	0.182
H(9C)	2*i*	0.4423	0.2223	0.5172	0.182
H(10A)	2*i*	0.2312	0.4262	0.4191	0.213
H(10B)	2*i*	0.1200	0.3147	0.4759	0.213
H(10C)	2*i*	0.0481	0.2859	0.3948	0.213
H(12)	2*i*	0.0777	0.0917	0.0503	0.059
H(13)	2*i*	–0.1671	0.2157	0.0028	0.059

Table 2. continued.

Atom	Site	x	y	z	U_{iso}
H(16)	2*i*	0.2223	0.4606	0.2022	0.050
H(19A)	2*i*	0.1973	0.7895	0.1743	0.095
H(19B)	2*i*	0.1554	0.7142	0.2487	0.095
H(19C)	2*i*	0.0532	0.8579	0.2229	0.095
H(20A)	2*i*	–0.2887	0.6696	0.2368	0.076
H(20B)	2*i*	–0.3341	0.4905	0.1990	0.076
H(21)	2*i*	–0.1163	0.4098	0.2851	0.104
H(22A)	2*i*	–0.2315	0.6627	0.3603	0.171
H(22B)	2*i*	–0.1361	0.5156	0.3931	0.171
H(3A)	2*i*	–0.3750	0.4177	0.0173	0.059

Table 3. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	2*i*	0.6186(4)	0.0261(4)	0.2986(2)	0.055(2)	0.085(2)	0.078(2)	0.028(1)	0.003(1)	0.022(2)
C(2)	2*i*	0.5425(3)	0.0828(3)	0.2345(1)	0.043(1)	0.054(1)	0.064(1)	0.018(1)	0.001(1)	0.011(1)
C(3)	2*i*	0.5904(4)	0.0528(3)	0.1671(1)	0.053(1)	0.062(1)	0.073(2)	0.028(1)	0.015(1)	0.013(1)
C(4)	2*i*	0.4603(3)	0.1127(3)	0.1201(1)	0.056(1)	0.058(1)	0.054(1)	0.023(1)	0.012(1)	0.007(1)
C(5)	2*i*	0.3318(3)	0.1784(2)	0.1586(1)	0.044(1)	0.039(1)	0.047(1)	0.0114(9)	0.0021(9)	0.0013(8)
C(6)	2*i*	0.2643(3)	0.1819(3)	0.2879(1)	0.052(1)	0.048(1)	0.046(1)	0.015(1)	0.001(1)	0.0030(9)
C(7)	2*i*	0.2918(5)	0.1922(5)	0.4188(1)	0.102(2)	0.138(3)	0.040(1)	0.044(2)	0.001(1)	0.002(2)
C(8)	2*i*	0.1870(6)	0.0093(6)	0.4218(2)	0.105(3)	0.149(4)	0.086(2)	0.016(3)	0.018(2)	0.052(2)
C(9)	2*i*	0.4765(6)	0.2356(6)	0.4687(2)	0.128(3)	0.179(4)	0.054(2)	0.038(3)	–0.023(2)	–0.005(2)
C(10)	2*i*	0.1610(8)	0.3159(7)	0.4279(2)	0.179(5)	0.205(5)	0.068(2)	0.109(4)	0.004(3)	–0.030(3)
C(11)	2*i*	0.1741(3)	0.2606(2)	0.1321(1)	0.043(1)	0.042(1)	0.043(1)	0.0130(9)	0.0029(8)	0.0022(8)
C(12)	2*i*	0.0564(3)	0.1899(3)	0.0720(1)	0.055(1)	0.048(1)	0.048(1)	0.021(1)	–0.001(1)	–0.0093(9)
C(13)	2*i*	–0.0920(3)	0.2629(3)	0.0437(1)	0.052(1)	0.053(1)	0.043(1)	0.016(1)	–0.0066(9)	–0.0101(9)
C(14)	2*i*	–0.1268(3)	0.4068(2)	0.0771(1)	0.043(1)	0.043(1)	0.041(1)	0.0130(9)	–0.0022(8)	0.0013(8)
C(15)	2*i*	–0.0101(3)	0.4816(2)	0.1373(1)	0.044(1)	0.0365(9)	0.040(1)	0.0092(8)	0.0013(8)	0.0016(8)
C(16)	2*i*	0.1413(3)	0.4093(2)	0.1633(1)	0.044(1)	0.039(1)	0.039(1)	0.0088(8)	–0.0035(8)	0.0004(8)
C(17)	2*i*	–0.2933(3)	0.6384(3)	0.0699(1)	0.055(1)	0.051(1)	0.047(1)	0.021(1)	–0.005(1)	0.0000(9)
C(18)	2*i*	–0.0695(3)	0.6307(3)	0.1732(1)	0.050(1)	0.042(1)	0.044(1)	0.0155(9)	–0.0048(9)	–0.0022(8)
C(19)	2*i*	0.0994(4)	0.7599(3)	0.2080(2)	0.068(2)	0.044(1)	0.075(2)	0.012(1)	–0.017(1)	–0.011(1)
C(20)	2*i*	–0.2319(4)	0.5742(3)	0.2242(1)	0.065(2)	0.070(2)	0.055(1)	0.019(1)	0.009(1)	–0.005(1)
C(21)	2*i*	–0.1689(5)	0.5053(4)	0.2895(2)	0.119(3)	0.075(2)	0.074(2)	0.037(2)	0.027(2)	0.010(2)
C(22)	2*i*	–0.1796(9)	0.5671(6)	0.3538(2)	0.240(6)	0.145(4)	0.066(2)	0.097(4)	0.039(3)	0.013(2)
N(1)	2*i*	0.6815(4)	–0.0261(4)	0.3485(2)	0.091(2)	0.143(3)	0.099(2)	0.057(2)	0.001(2)	0.048(2)
N(2)	2*i*	0.3817(2)	0.1621(2)	0.23036(9)	0.0409(9)	0.0456(9)	0.048(1)	0.0140(8)	–0.0001(7)	0.0023(7)
N(3)	2*i*	–0.2813(3)	0.4798(2)	0.0523(1)	0.050(1)	0.049(1)	0.051(1)	0.0199(8)	–0.0119(8)	–0.0064(8)
O(1)	2*i*	0.3777(3)	0.2121(2)	0.34742(8)	0.068(1)	0.085(1)	0.0448(9)	0.015(1)	–0.0036(8)	–0.0013(8)
O(2)	2*i*	0.0917(2)	0.1707(2)	0.27977(9)	0.053(1)	0.080(1)	0.0540(9)	0.0252(9)	0.0082(7)	0.0073(8)
O(3)	2*i*	–0.1558(2)	0.7238(2)	0.11814(8)	0.062(1)	0.0423(8)	0.0569(9)	0.0198(7)	–0.0101(8)	–0.0021(7)
O(4)	2*i*	–0.4166(3)	0.7087(2)	0.04320(9)	0.072(1)	0.064(1)	0.064(1)	0.0354(9)	–0.0155(9)	–0.0039(8)

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