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Pimobendan B from powder diffraction data

Alvis Zvirgzdins,[a]* Mara Delina,[a] Anatoly Mishnev[b] and Andris Actins[a]

[a]University of Latvia, Department of Chemistry, Kr. Valdemara Street 48, Riga, LV-1013, Latvia, and [b]Latvian Institute of Organic Synthesis, Aizkraukles Street 21, Riga, LV-1006, Latvia
Correspondence e-mail: alvis.zvirgzdins@lais.lv

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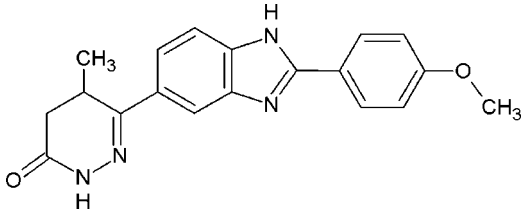
Key indicators: powder X-ray study; T = 293 K; mean σ(C–C) = 0.003 Å; R factor = 0.019; wR factor = 0.026; data-to-parameter ratio = 49.6.

The title molecule, $C_{19}H_{18}N_4O_2$ {systematic name: (*RS*)-6-[2-(4-methoxyphenyl)-1*H*-benzimidazol-5-yl]-5-methyl-4,5-dihydropyridazin-3(2*H*)-one}, adopts an extended conformation. The dihedral angles between the central benzimidazole ring sytem and the pendant methoxyphenyl and pyridazinone residues are 1.41 (18) and 9.7 (3)°, respectively. In the crystal, N—H···N hydrogen bonds link the imadazole groups into [001] chains, and pairs of N—H···O hydrogen bonds link the pyridazinone groups into dimers. Together, these generate a two-dimensional supramolecular structure parallel to (010). The layers are linked by C—H···π interactions.

Related literature

For general information about pimobendan, see: Gordon *et al.* (2006). For related crystalline forms, see: Boeren *et al.* (2011). Semi-empirical calculations were carried out with *HYPERCHEM Professional* (Hypercube, 2010). Refinement of lattice parameters and peak profile determination were performed by Le Bail profile fitting (Le Bail *et al.*, 1988)



Experimental

Crystal data

$C_{19}H_{18}N_4O_2$
M_r = 334.37
Monoclinic, $P2_1/c$
a = 18.891 (5) Å
b = 9.9619 (5) Å
c = 9.5029 (8) Å
β = 90.799 (13)°
V = 1788.2 (5) Å^3
Z = 4
Cu $K\alpha$ radiation
λ = 1.54184 Å
μ = 0.68 mm^{-1}
T = 293 K
cylinder, 16 × 0.5 mm

Data collection

Bruker D8 diffractometer
Specimen mounting: capillary
Data collection mode: transmission
Scan method: step
$2\theta_{min}$ = 3.5°, $2\theta_{max}$ = 70.00°, $2\theta_{step}$ = 0.01°

Refinement

R_p = 0.019
R_{wp} = 0.026
R_{exp} = 0.020
R_{Bragg} = 0.015
χ^2 = 1.690
6651 data points
134 parameters
56 restraints
H-atom parameters not refined

Table 1
Hydrogen-bond geometry (Å, °).

*Cg*1 is the centroid of the C12/C20/C15/C24/C22/C21 ring.

D—H···A	D—H	H···A	D···A	D—H···A
N3—H42···O9^{i}	0.97	1.85	2.817 (3)	174
N11—H43···N1^{ii}	0.95	2.27	3.2039 (19)	168
C18—H26···*Cg*1^{iii}	0.97	2.43	3.369 (2)	161

Symmetry codes: (i) $-x+1, -y+1, -z$; (ii) $x, -y+\frac{3}{2}, z+\frac{1}{2}$; (iii) $-x, y-\frac{1}{2}, -z-\frac{1}{2}$.

Data collection: *Dicvol* (Boultif & Louër, 2004); cell refinement: *FOX* (Favre-Nicolin & Černý, 2002); data reduction: *FOX*; program(s) used to solve structure: *FOX*; program(s) used to refine structure: *FULLPROF* (Rodriguez-Carvajal, 1993), *CRYSTALS* (Betteridge *et al.*, 2003) and *PLATON* (Spek, 2009); molecular graphics: *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *WinPlotr* (Roisnel & Rodriguez-Carvajal, 2000) and *publCIF* (Westrip, 2010).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HB7139).

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supporting information

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Pimobendan B from powder diffraction data

Alvis Zvirgzdins, Mara Delina, Anatoly Mishnev and Andris Actins

S1. Experimental

Indexing of patterns was performed with *WinPlotr* (Roisnel & Rodriguez-Carvajal, 2000) and *Dicvol* (Boultif & Louër, 2004) using reflections in the 2θ range of 3.00 – 30.00°. Space groups for all polymorphs were determined using *FOX 1.9.7.0* (Favre-Nicolin & Černý, 2002). The correct space group was selected based on possible systematic extinctions. The compositions of unit cell and the values of Z were determined in all cases from the unit cell volume.

Refinement of lattice parameters and peak profile determination were performed by Le Bail profile fitting (Le Bail *et al.*, 1988) using *FOX*. Structures were determined with *FOX* by parallel tempering algorithm. The best cost function values were reached by using automatic temperature schedule and Cauchy-type displacement amplitude schedule.

The input model of pimobendan molecule was obtained from semiempirical calculations by *HYPERCHEM Professional* (Hypercube, 2010) for both - R and S enentiomer. The molecules were described in terms of Fenske-Hall Z-matrix format ans structure solutions The dihedral angles C21—C22—O7—C25; N11—C8—C20—C15 and C2—C6—C14—N4 were defined as intramolecular degrees of freedom and were varied during the structure determinations.

S1.1. Synthesis and crystallization

Pimobendan form B was prepared in three steps. At the first step, its dioxane solvate was held in a thermostat at 100°C for one day. At the second step obtained powder were suspended in methanol and suspension were hold in a dry box while all methanol evaporates. At the end obtained methanol solvate were desolvatated at 100°C.

S1.2. Refinement

Rietveld refinement for the final structure was performed by *Fullprof*. Hydrogen atoms were added with *Crystals* according to the molecular geometry and their positions were not refined. Since the bond lengths and angles departed to unacceptable values, atomic parameters for (N3, N4, C5, O9, C14, C16, C17,C23), (N1, N11, C2, C6, C8, C10, C13, C18, C19) and (O7, C12, C15, C20, C21, C22, C24, C25) were refined as rigid bodies.

S2. Results and discussion

Several crysltalline forms of pimobendan and its preparation are patented (Boeren *et al.*, 2011) but there are no crystal data for these polymorphs or pseudopolymorhs. This article is focused on the structure determination from powder data and description of the pimobendan B form.

Lowest value of cost function were obtained by using molecular model of R enantiomer in structure determination process. The final structure of pimobendane B form shows that pimobendane molecule is almost linear because the dihedral angle value of N11—C8—C20—C15 = 9.7 (3)° and C13—C6—C14—N4 = 1.41 (18)°. The crystal structure of title compound consist of molecules that are conected via hydrogen bonds that are formed between two imidazole groups (N11—H43···N1^{ii}) and two dihydropyradazinone groups (N3—H42···O9^{i} and N3^{i}—H42···O9). There are T-shaped C—H···π stacking interactions between benzol in methoxyphenyl and benzimidazol groups.

Modeling with PLATON (Spek, 2009) showed that the crystal structure contain voids (69Å^3) accessible to solvent molecules. Since pimobendan B form are obtained from its methanol solvate by desolvation at 100°C, these voids may be result of desolvation at temperature that is almost twice as large as boiling point this solvent. Pimobendan B form at ambient conditions tends to form monohydrate. Unstabilty of pimobendane B form at ambient conditions may be explained by penetration of water molecules into voids of crystal structure.

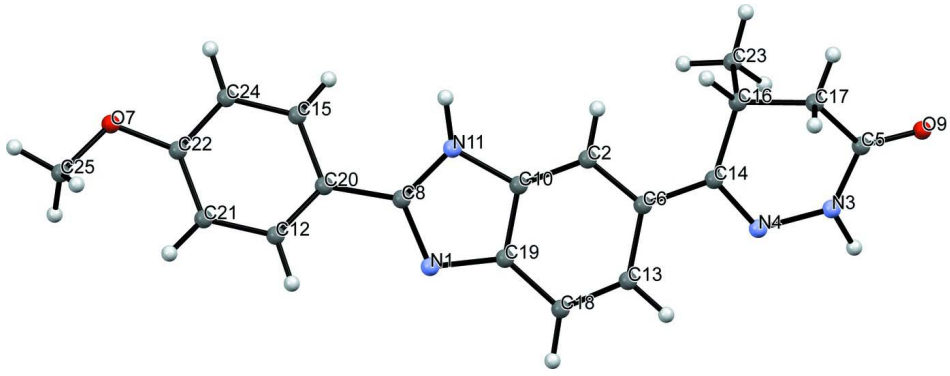

Figure 1

The molecular structure of the title compound showing 50% probability ellipsoids and hydrogen atoms are shown as small spheres of arbitrary radii.

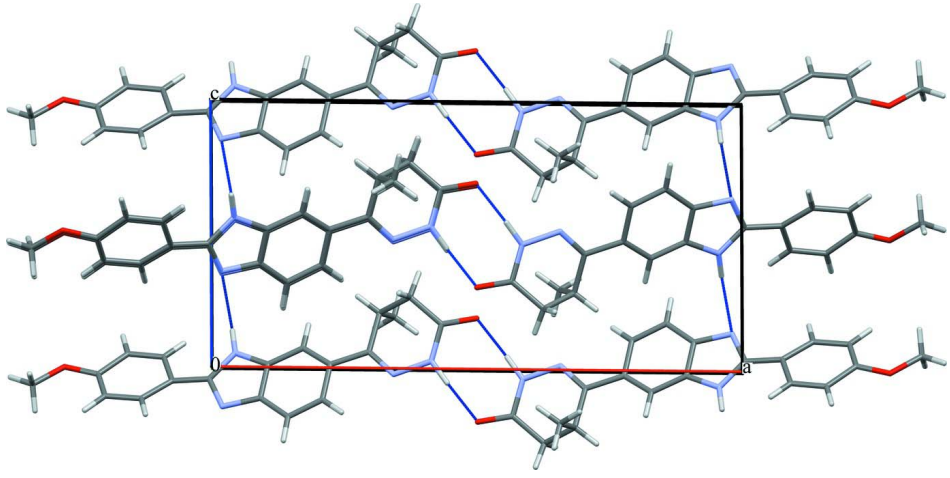

Figure 2

Packing diagram of the title compound viewed along the *b* axis. Blue lines indicate hydrogen bonds.

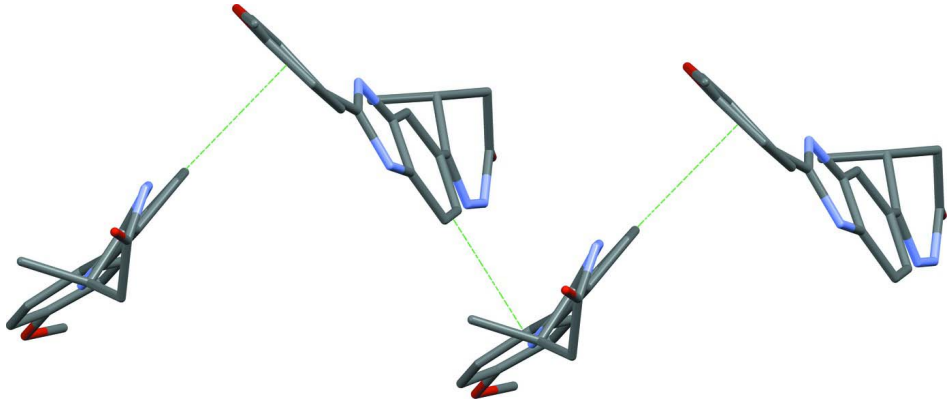

Figure 3

Stacking interactions in the crystal structure of title compound

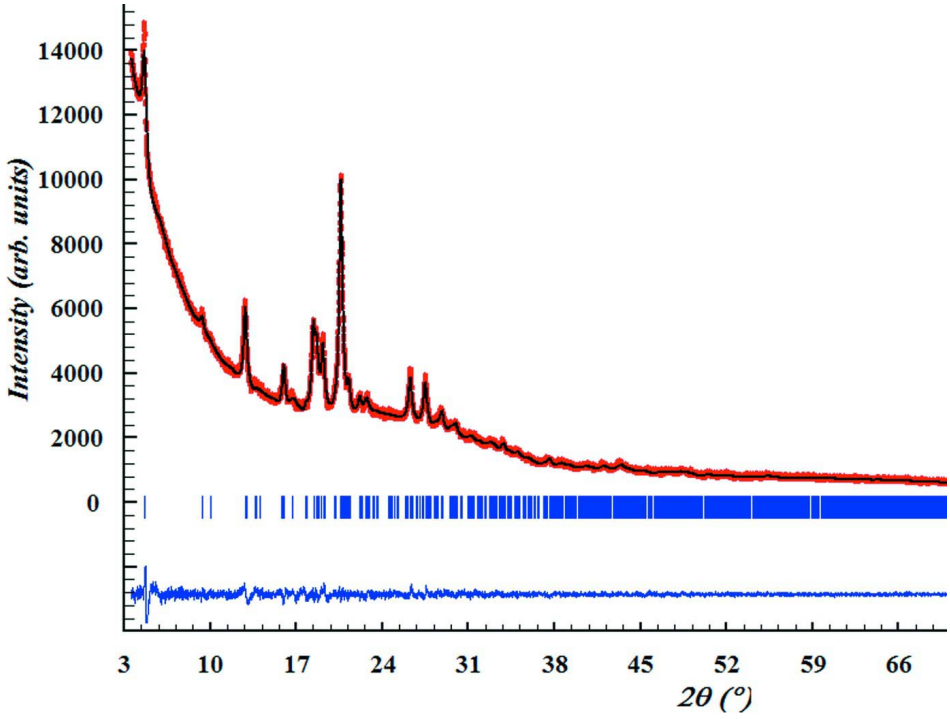

Figure 4

Scattered X-ray intensities of title compound at ambient conditions as a function of diffraction angle 2θ. The observed pattern (red dots), the best Rietveld fit profiles (line) and the difference curve between the observed and calculated profiles (below) are shown.

(*RS*)-6-[2-(4-Methoxyphenyl)-1*H*-benzimidazol-5-yl]-5-methyl-4,5-dihydropyridazin-3(2*H*)-one

Crystal data

$C_{19}H_{18}N_4O_2$
M_r = 334.37
Monoclinic, $P2_1/c$
Hall symbol: -P 2ybc
a = 18.891 (5) Å
b = 9.9619 (5) Å
c = 9.5029 (8) Å
β = 90.799 (13)°
V = 1788.2 (5) Å^3
Z = 4
D_x = 1.24 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å

μ = 0.68 mm^{-1}
T = 293 K

white
cylinder, 16 × 0.5 mm

Data collection

Bruker D8 diffractometer
Radiation source: sealed X-ray tube
None monochromator

Specimen mounting: capillary
Data collection mode: transmission
Scan method: step
$2\theta_{min}$ = 3.5°, $2\theta_{max}$ = 70.00°, $2\theta_{step}$ = 0.01°

Refinement

Refinement on I_{net}
Least-squares matrix: full
R_p = 0.019
R_{wp} = 0.026
R_{exp} = 0.020
R_{Bragg} = 0.015
χ^2 = 1.690
6651 data points
Profile function: Pseudo Voigt

134 parameters
56 restraints
75 constraints
Hydrogen site location: inferred from neighbouring sites
H-atom parameters not refined

$(\Delta/\sigma)_{max}$ = 0.01
Background function: linear extrapolation

Special details

Refinement. Rietveld refinement for the final structure was performed by *Fullprof*. Hydrogen atoms were added with *Crystals* according to the molecular geometry and their positions were not refined, but final refinement was performed with hydrogen atoms. Since the bond lengths and angles departed to unacceptable values, atomic parameters for (N3, N4, C5, O9, C14, C16, C17,C23), (N1, N11, C2, C6, C8, C10, C13, C18, C19) and (O7, C12, C15, C20, C21, C22, C24, C25) were refined as rigid bodies.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	0.01915 (12)	0.62643 (12)	−0.14418 (12)	0.01267*
C2	0.17167 (12)	0.65440 (12)	0.07706 (12)	0.01267*
N3	0.41366 (13)	0.52345 (13)	0.03230 (13)	0.01267*
N4	0.34263 (13)	0.53781 (13)	−0.01834 (13)	0.01267*
C5	0.43319 (13)	0.53662 (13)	0.17085 (13)	0.01267*
C6	0.22286 (12)	0.58183 (12)	0.01645 (12)	0.01267*
O7	−0.27870 (17)	0.93069 (17)	0.00050 (17)	0.01267*
C8	−0.00564 (12)	0.70860 (12)	−0.04114 (12)	0.01267*
O9	0.49920 (13)	0.54750 (13)	0.19404 (13)	0.01267*
C10	0.10535 (12)	0.66256 (12)	0.01531 (12)	0.01267*
N11	0.04376 (12)	0.73283 (12)	0.05732 (12)	0.01267*
C12	−0.13383 (17)	0.70975 (17)	−0.11682 (17)	0.01267*
C13	0.20788 (12)	0.51835 (12)	−0.11605 (12)	0.01267*
C14	0.29607 (13)	0.58849 (13)	0.06534 (13)	0.01267*
C15	−0.09123 (17)	0.88148 (17)	0.04048 (17)	0.01267*
C16	0.31636 (13)	0.63793 (13)	0.21183 (13)	0.01267*
C17	0.37363 (13)	0.54600 (13)	0.27154 (13)	0.01267*
C18	0.14285 (12)	0.52292 (12)	−0.18095 (12)	0.01267*
C19	0.09089 (12)	0.59914 (12)	−0.11154 (12)	0.01267*
C20	−0.07552 (17)	0.77153 (17)	−0.04901 (17)	0.01267*
C21	−0.20225 (17)	0.76004 (17)	−0.10811 (17)	0.01267*

C22	−0.21504 (17)	0.87352 (17)	−0.02608 (17)	0.01267*
C23	0.34340 (13)	0.78483 (13)	0.19844 (13)	0.01267*
C24	−0.15891 (17)	0.93136 (17)	0.05152 (17)	0.01267*
C25	−0.33907 (17)	0.86902 (17)	−0.06608 (17)	0.01267*
H26	0.13416	0.47697	−0.26987	0.0152*
H27	0.24355	0.46651	−0.16258	0.0152*
H28	0.18217	0.69913	0.16336	0.0152*
H29	−0.05380	0.92376	0.09189	0.0152*
H30	−0.16806	1.00299	0.11652	0.0152*
H31	−0.24066	0.72624	−0.16210	0.0152*
H32	−0.12618	0.63253	−0.17586	0.0152*
H33	−0.38045	0.92304	−0.04037	0.0152*
H34	−0.34437	0.78145	−0.02928	0.0152*
H35	−0.33452	0.86891	−0.16468	0.0152*
H36	0.27557	0.63704	0.27202	0.0152*
H37	0.35319	0.45789	0.28346	0.0152*
H38	0.39052	0.57826	0.36071	0.0152*
H39	0.35524	0.82003	0.29000	0.0152*
H40	0.30710	0.84168	0.15603	0.0152*
H41	0.38474	0.78628	0.14061	0.0152*
H42	0.44322	0.50470	−0.04847	0.0152*
H43	0.03860	0.78640	0.13920	0.0152*

Geometric parameters (Å, º)

O7—C22	1.358 (4)	C16—C23	1.556 (2)
O7—C25	1.435 (4)	C16—C17	1.521 (3)
O9—C5	1.268 (3)	C18—C19	1.412 (3)
N1—C8	1.3642 (19)	C21—C22	1.396 (2)
N1—C19	1.413 (3)	C22—C24	1.407 (4)
N3—N4	1.426 (3)	C2—H28	0.95
N3—C5	1.3687 (19)	N3—H42	0.97
N4—C14	1.296 (3)	N11—H43	0.95
N11—C8	1.334 (3)	C12—H32	0.96
N11—C10	1.420 (3)	C13—H27	0.96
C2—C6	1.344 (3)	C15—H29	0.95
C2—C10	1.378 (3)	C16—H36	0.97
C5—C17	1.490 (3)	C17—H37	0.97
C6—C14	1.454 (3)	C17—H38	0.96
C6—C13	1.4337 (17)	C18—H26	0.97
C8—C20	1.462 (4)	C21—H31	0.94
C10—C19	1.3848 (17)	C23—H39	0.96
C12—C20	1.410 (4)	C23—H40	0.97
C12—C21	1.390 (4)	C23—H41	0.96
C13—C18	1.368 (3)	C24—H30	0.96
C14—C16	1.5207 (19)	C25—H33	0.98
C15—C24	1.377 (4)	C25—H34	0.95
C15—C20	1.421 (3)	C25—H35	0.94

C22—O7—C25	116.05 (17)	C14—C16—C17	108.38 (13)
C8—N1—C19	107.21 (14)	C14—C16—C23	107.98 (10)
N4—N3—C5	123.69 (18)	C17—C16—C23	111.36 (18)
N3—N4—C14	118.38 (14)	C5—C17—C16	109.74 (12)
C8—N11—C10	106.35 (12)	C13—C18—C19	115.67 (12)
N4—N3—H42	107.00	N1—C19—C18	132.23 (13)
C5—N3—H42	129.00	C10—C19—C18	121.47 (19)
C10—N11—H43	127.00	N1—C19—C10	106.28 (15)
C8—N11—H43	127.00	C8—C20—C12	122.36 (16)
C6—C2—C10	120.30 (13)	C8—C20—C15	119.7 (2)
O9—C5—C17	129.25 (14)	O7—C22—C21	127.2 (3)
N3—C5—C17	115.3 (2)	C10—C2—H28	121.00
O9—C5—N3	115.26 (18)	C6—C13—H27	121.00
C13—C6—C14	118.42 (17)	C15—C24—C22	120.41 (18)
C2—C6—C13	118.65 (19)	C12—C21—C22	119.6 (2)
C2—C6—C14	121.70 (13)	C21—C22—C24	119.3 (3)
N11—C8—C20	125.48 (14)	C6—C2—H28	119.00
N1—C8—C20	122.63 (16)	C20—C12—H32	119.00
N1—C8—N11	111.60 (19)	C20—C15—H29	119.00
N11—C10—C19	108.49 (17)	C24—C15—H29	119.00
C2—C10—C19	120.71 (17)	C21—C12—H32	118.00
N11—C10—C2	130.76 (12)	C12—C20—C15	116.2 (3)
C20—C12—C21	122.47 (18)	C18—C13—H27	116.00
C6—C13—C18	123.12 (17)	O7—C22—C24	113.20 (18)
N4—C14—C6	115.89 (14)	C14—C16—H36	110.00
C6—C14—C16	122.25 (17)	C17—C16—H36	110.00
N4—C14—C16	121.6 (2)	C23—C16—H36	109.00
C20—C15—C24	121.7 (2)	C5—C17—H37	109.00

Hydrogen-bond geometry (Å, º)

Cg1 is the centroid of the C12/C20/C15/C24/C22/C21 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H42···O9^{i}	0.97	1.85	2.817 (3)	174
N11—H43···N1^{ii}	0.95	2.27	3.2039 (19)	168
C18—H26···*Cg*1^{iii}	0.97	2.43	3.369 (2)	161

Symmetry codes: (i) −*x*+1, −*y*+1, −*z*; (ii) *x*, −*y*+3/2, *z*+1/2; (iii) −*x*, *y*−1/2, −*z*−1/2.