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A New Non-Peptide Angiotensin II Receptor Antagonist

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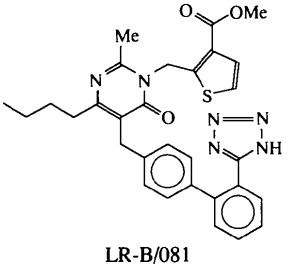
Abstract

The structure of methyl 2-[(4-butyl-2-methyl-6-oxo-5-{4-[2-(1*H*-tetrazol-5-yl)phenyl]benzyl}-1*H*-pyrimidin-1-yl)methyl]-3-thiophenecarboxylate (LR-B/081), $C_{30}H_{30}N_6O_3S$, has been established by X-ray analysis. Partial disorder is observed in the terminal portion of the alkyl chain bonded to the pyrimidinone ring; the six atoms of the latter are coplanar to within 0.008 (2) Å. The crystal structure consists of infinite ribbons of molecules extended along the *c* axis of the orthorhombic cell (space group *Pbca*). Molecules within the ribbon are connected pairwise by an N—H···N hydrogen bond between the tetrazole and the pyrimidinone rings, with an N···N separation of 2.900 (3) Å.

Comment

The role of the renin–angiotensin system (RAS) and its importance in the regulation of blood pressure in humans are now well established (Valloton, 1987). The most recent research in this field has focused on the synthesis of receptor antagonists of the octapeptide hormone angiotensin II (see, for example, Carini *et al.*, 1991). As part of this synthetic effort, the compound LR-B/081 has been obtained recently (Scolastico & Salimbeni, 1994), and is currently undergoing clinical evaluation (in phase I/II trials) and development for the treatment of hypertension. The room-temperature structural study of this novel angiotensin II receptor antagonist has been undertaken as a preliminary step in the detailed investigation of its electrostatic properties, which we plan to perform again [as in our previous study of L-alanine (Destro, Bianchi & Morosi, 1989)] by X-ray diffraction at a temperature below 25 K.



LR-B/081

The numbering scheme adopted in the present analysis is shown in Fig. 1. The butyl chain at the C1 position was found to be disordered and several models for this were tested during the refinement. The final interpretation of the disorder implies two ethyl groups at C28, with the four atoms C29*A*, C29*B*, C30*A* and C30*B*, and their corresponding H atoms, having equal site occupancies of 0.5. The dihedral angle between the two phenyl rings of the biphenyl moiety is 51.3 (4)°, while the tetrazole ring forms an angle of 57.5 (4)° with the phenyl ring to which it is bonded. Such a staggered conformation of the three rings closely resembles that reported for DUP753, a prototypical compound of the same class of drugs (Johnson *et al.*, 1990).

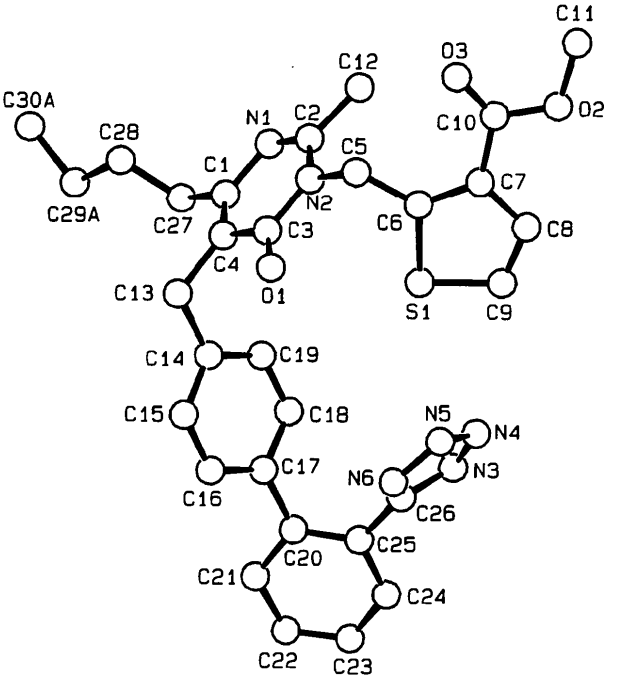


Fig. 1. A view of LR-B/081 showing the atom-labelling scheme. Only the *A* conformation of the disordered butyl chain is shown. H atoms are omitted for clarity.

Experimental

Crystal data

$C_{30}H_{30}N_6O_3S$
M_r = 554.66
Orthorhombic
Pbca
a = 30.328 (3) Å
b = 15.279 (2) Å
c = 12.499 (4) Å
V = 5792 (2) Å^3
Z = 8
D_x = 1.272 Mg m^{-3}
Mo *Kα* radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 9.0–12.0°
μ = 0.145 mm^{-1}
T = 293 (2) K
Prism
0.350 × 0.175 × 0.075 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω scans
Absorption correction: none
3778 measured reflections
3778 independent reflections
1536 observed reflections [$I > 2\sigma(I)$]
$\theta_{max} = 22.47°$
$h = 0 \rightarrow 32$
$k = 0 \rightarrow 16$
$l = 0 \rightarrow 13$
3 standard reflections
frequency: 120 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0777$
$wR(F^2) = 0.1281$
$S = 1.279$
3778 reflections
363 parameters
$w = 1/[\sigma^2(F_o^2) + (0.0486P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.253$
$\Delta\rho_{max} = 0.274$ e Å^{-3}
$\Delta\rho_{min} = -0.191$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters* (Å^2)

U_{iso} for disordered C29–30; $U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$ for others.

	x	y	z	U_{iso}/U_{eq}
S1	0.02846 (4)	0.14608 (6)	0.25053 (9)	0.0679 (3)
O1	0.02915 (8)	0.3107 (2)	0.0899 (2)	0.0696 (9)
O2	−0.08366 (8)	0.1497 (2)	0.5239 (2)	0.0845 (10)
O3	−0.08249 (9)	0.2793 (2)	0.4436 (2)	0.1109 (12)
N1	0.08190 (8)	0.4365 (2)	0.3426 (2)	0.0453 (9)
N2	0.02587 (8)	0.3523 (2)	0.2641 (2)	0.0429 (8)
N3	0.15092 (10)	−0.0374 (2)	0.1866 (2)	0.0741 (11)
N4	0.10656 (11)	−0.0369 (2)	0.2044 (2)	0.0772 (12)
N5	0.08562 (9)	−0.0119 (2)	0.1199 (2)	0.0633 (10)
N6	0.11693 (8)	0.0031 (2)	0.0455 (2)	0.0527 (9)
C1	0.10347 (10)	0.4383 (2)	0.2434 (3)	0.0429 (10)
C2	0.04484 (11)	0.3940 (2)	0.3490 (3)	0.0430 (11)
C3	0.04612 (12)	0.3512 (2)	0.1623 (3)	0.0536 (12)
C4	0.08689 (11)	0.3993 (2)	0.1577 (3)	0.0449 (11)
C5	−0.01586 (10)	0.3045 (2)	0.2738 (3)	0.0462 (11)
C6	−0.01057 (10)	0.2121 (2)	0.3091 (3)	0.0422 (11)
C7	−0.03325 (10)	0.1672 (2)	0.3862 (3)	0.0470 (11)
C8	−0.01876 (12)	0.0808 (2)	0.3969 (3)	0.0629 (13)
C9	0.01381 (12)	0.0599 (2)	0.3301 (3)	0.0697 (15)
C10	−0.06869 (11)	0.2076 (3)	0.4529 (3)	0.0622 (13)
C11	−0.11848 (12)	0.1824 (3)	0.5914 (3)	0.104 (2)
C12	0.02285 (11)	0.3861 (2)	0.4545 (3)	0.0598 (13)
C13	0.10860 (12)	0.3954 (2)	0.0470 (3)	0.0603 (13)
C14	0.13404 (10)	0.3114 (2)	0.0296 (3)	0.0463 (11)
C15	0.14550 (10)	0.2836 (2)	−0.0724 (2)	0.0485 (11)
C16	0.17098 (11)	0.2095 (2)	−0.0872 (3)	0.0557 (12)
C17	0.18470 (10)	0.1585 (2)	−0.0028 (3)	0.0468 (11)
C18	0.17277 (11)	0.1852 (2)	0.0989 (3)	0.0610 (13)
C19	0.14766 (12)	0.2601 (2)	0.1129 (3)	0.0623 (12)
C20	0.21111 (10)	0.0774 (2)	−0.0178 (3)	0.0605 (13)
C21	0.24994 (12)	0.0799 (3)	−0.0801 (3)	0.0799 (15)
C22	0.27538 (13)	0.0032 (3)	−0.0870 (3)	0.104 (2)
C23	0.26354 (14)	−0.0713 (3)	−0.0361 (4)	0.112 (2)
C24	0.22532 (12)	−0.0745 (3)	0.0204 (4)	0.094 (2)
C25	0.19849 (11)	−0.0014 (2)	0.0304 (3)	0.0597 (12)
C26	0.15634 (11)	−0.0122 (2)	0.0871 (3)	0.0497 (12)
C27	0.14637 (10)	0.4871 (2)	0.2435 (3)	0.0575 (12)
C28	0.14415 (10)	0.5831 (2)	0.2217 (4)	0.089 (2)
C29*A*†	0.1926 (2)	0.6170 (3)	0.1993 (7)	0.085 (3)
C30*A*†	0.1923 (4)	0.7143 (4)	0.2269 (10)	0.188 (5)
C29*B*†	0.1885 (2)	0.6295 (3)	0.2392 (6)	0.098 (3)
C30*B*†	0.1962 (3)	0.7072 (4)	0.1667 (7)	0.139 (4)

† Site occupancy = 0.5.

Table 2. *Selected geometric parameters* (Å, °)

S1—C9	1.710 (4)	C1—C27	1.499 (4)
S1—C6	1.719 (3)	C2—C12	1.483 (4)
O1—C3	1.212 (4)	C3—C4	1.439 (5)
O2—C10	1.333 (4)	C4—C13	1.534 (5)
O2—C11	1.441 (4)	C5—C6	1.489 (4)
O3—C10	1.178 (4)	C6—C7	1.368 (4)
N1—C2	1.301 (4)	C7—C8	1.398 (5)
N1—C1	1.402 (4)	C7—C10	1.494 (5)
N2—C2	1.365 (4)	C8—C9	1.332 (5)
N2—C3	1.413 (4)	C13—C14	1.512 (4)
N2—C5	1.466 (4)	C17—C20	1.488 (5)
N3—C26	1.312 (4)	C27—C28	1.493 (4)
N3—N4	1.363 (4)	C28—C29*B*	1.535 (5)
N4—N5	1.290 (4)	C28—C29*A*	1.584 (5)
N5—N6	1.349 (4)	C29*A*—C30*A*	1.526 (6)
N6—C26	1.324 (4)	C29*B*—C30*B*	1.513 (7)
C1—C4	1.324 (5)		
C9—S1—C6	91.4 (2)	C6—C7—C8	112.5 (3)
C10—O2—C11	114.2 (3)	C6—C7—C10	123.2 (3)
C2—N1—C1	117.9 (3)	C8—C7—C10	124.3 (3)
C2—N2—C3	121.5 (3)	C9—C8—C7	113.6 (3)
C2—N2—C5	122.1 (3)	C8—C9—S1	111.9 (3)
C3—N2—C5	116.4 (3)	O3—C10—O2	124.2 (4)
C26—N3—N4	106.0 (3)	O3—C10—C7	125.8 (4)
N5—N4—N3	110.7 (3)	O2—C10—C7	110.0 (3)
N4—N5—N6	105.6 (3)	C14—C13—C4	112.5 (3)
C26—N6—N5	109.5 (3)	C19—C14—C13	122.1 (3)
C4—C1—N1	121.9 (3)	C15—C14—C13	121.3 (3)
C4—C1—C27	123.6 (3)	C16—C17—C20	122.5 (3)
N1—C1—C27	114.4 (3)	C18—C17—C20	120.1 (3)
N1—C2—N2	123.3 (3)	C25—C20—C17	121.0 (3)
N1—C2—C12	118.9 (3)	C21—C20—C17	119.7 (3)
N2—C2—C12	117.7 (3)	C24—C25—C26	117.6 (3)
O1—C3—N2	119.6 (3)	C20—C25—C26	122.8 (3)
O1—C3—C4	126.6 (3)	N3—C26—N6	108.1 (3)
N2—C3—C4	113.8 (3)	N3—C26—C25	126.8 (3)
C1—C4—C3	121.6 (3)	N6—C26—C25	125.1 (3)
C1—C4—C13	125.7 (3)	C28—C27—C1	116.7 (3)
C3—C4—C13	112.6 (3)	C27—C28—C29*B*	112.9 (3)
N2—C5—C6	113.9 (2)	C27—C28—C29*A*	108.2 (3)
C7—C6—C5	129.1 (3)	C30*A*—C29*A*—C28	105.8 (5)
C7—C6—S1	110.6 (2)	C30*B*—C29*B*—C28	114.4 (6)
C5—C6—S1	120.3 (2)		

The ethyl chain at C28 is disordered and has been split into two groups (C29*A*, C30*A* and C29*B*, C30*B* and the related H atoms). These C atoms were refined isotropically with the restraint that the U_{eq} values for C29*A* and C29*B* should be similar, and that the U_{eq} values for C30*A* and C30*B* should be similar. All parameters were refined for atom H6 (bonded to N6). All other H atoms were kept in calculated positions with $U_{iso} = kU_{eq}$, where U_{eq} is the equivalent displacement parameter of the atom to which the H atom is bonded and k was assumed to be 1.5 for methyl H atoms and 1.2 for the remaining H atoms. Possible reasons for the relatively high value of R include the rather poor quality of the crystal specimen, the disorder of the butyl chain (probably only partially allowed for by our model) and the above average thermal motion of several outermost atoms, with U_{eq} values > 0.09 Å^2 (see Table 1).

Data collection: *SDP* (Frenz, 1983). Cell refinement: *SDP*. Data reduction: *SDP*. Program(s) used to solve structure: *MULTAN*11/82 (Main *et al.*, 1982). Program(s) used to refine structure: *SDP* and *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1145). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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3-Amino-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide Monohydrate and 3-*tert*-Butyl-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-Dioxide

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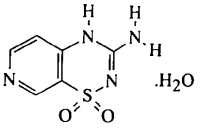
Abstract

The title compounds, $C_6H_6N_4O_2S.H_2O$, (I), and $C_{10}H_{13}N_3O_2S$, (II), were prepared for structural and pharmacological comparison with diazoxide, an antihypertensive agent. The crystal structure determinations show that the 4*H*- (rather than the 2*H*-) tautomeric form is preferentially adopted by these pyridothiadiazine derivatives in the solid state, as has also been found for diazoxide and other 1,2,4-thiadiazine 1,1-dioxide analogues. The *tert*-butyl moiety in (II) is slightly disordered.

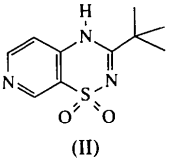
Comment

3-Amino-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide monohydrate, (I), is a heterocyclic compound for which the synthesis and the biological evaluation on insulin-secreting cells in comparison with diazoxide [7-chloro-3-methyl-2*H*(or 4*H*)-1,2,4-benzothiadiazine 1,1-dioxide] has recently been reported (Pirotte *et al.*, 1993). In the crystalline state, the thiadiazine and water molecules are linked by the hydrogen bonds N4—H4···O3 [N4···O3 2.676 (3), H4···O3 1.69 (2) Å, N4—H4···O3 165 (1)°], N11—H111···O2^{i} [N11···O2^{i} 3.100 (3), H111···O2^{i} 2.39 (2) Å, N11—H111···O2^{i} 134 (1)°], N11—H112···O1^{ii} [N11···O1^{ii} 2.959 (3), H112···O1^{ii} 2.13 (2) Å, N11—H112···O1^{ii} 162 (2)°], O3—H31···O2^{iii} [O3···O2^{iii} 2.841 (4), H31···O2^{iii} 1.87 (3) Å, O3—H31···O2^{iii} 172 (1)°] and O3—H32···N8^{iv} [O3···N8^{iv} 2.730 (3), H32···N8^{iv} 1.76 (2) Å, O3—H32···N8^{iv} 180 (1)°] [symmetry codes: (i) $\frac{1}{2}-x$, $-\frac{1}{2}+y$, $-z$; (ii) $-x$, $-y$, $-z$; (iii) $1-x$, $-y$, $-z$; (iv) $\frac{3}{2}-x$, $-\frac{1}{2}+y$, $1-z$].



(I)

3-*tert*-Butyl-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide, (II), was also investigated in order to compare its molecular structure with that of diazoxide. An article describing the preparation and the synthesis of the product, and the biological evaluation, is in preparation (Pirotte *et al.*, 1995). The molecules are linked by the hydrogen bond N4—H4···O1^{i} [N4···O1^{i} 2.981 (4), H4···O1^{i} 2.08 (2) Å, N4—H4···O1^{i} 156 (1)°; symmetry code: (i) $\frac{1}{2}-x$, $-\frac{1}{2}+y$, $1-z$].



(II)

In both crystal structures the N2—C3 and N4—C3 bond lengths, the location of the H atom on N4 rather than on N2, and the hydrogen-bonding schemes indicate that the 4*H*- form is favoured in the solid state. The same conclusion has been drawn for diazoxide