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Pyrazolidine-3,5-dione angiotensin-II receptor antagonists

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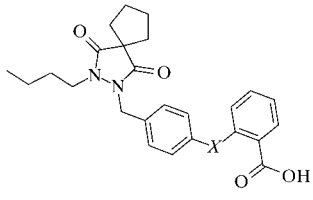
The crystal structures of three angiotensin-II receptor antagonists involving different spacer groups (CO, CONH and NHCO) between the aryl rings are presented, namely 2-{4-[(3-butyl-1,4-dioxo-2,3-diazaspiro[4.4]non-2-yl)methyl]-benzoyl}benzoic acid, $C_{26}H_{28}N_2O_5$, (I), 2-{4-[(3-butyl-1,4-dioxo-2,3-diazaspiro[4.4]non-2-yl)methyl]benzamido}benzoic acid, $C_{26}H_{29}N_3O_5$, (II), and 2-{4-[(3-butyl-1,4-dioxo-2,3-diazaspiro[4.4]non-2-yl)methyl]anilinocarbonyl}benzoic acid monohydrate, $C_{26}H_{29}N_3O_5\cdot H_2O$, (III). The aryl rings of (II) are almost coplanar, in contrast with compounds (I) and (III). The conformation of (II) is induced by an intramolecular N—H···O hydrogen bond between the amide and carboxylic acid groups.

Comment

The renin–angiotensin system (RAS) plays an important role in the regulation of blood pressure and electrolyte balance. Non-peptide AT1-selective angiotensin-II receptor antagonists which block the RAS are of great interest in the treatment of hypertension and other cardiovascular diseases (Wexler *et al.*, 1996). Recently, we reported new pyrazolidine-3,5-dione derivatives displaying AT1-binding affinity (Le Bourdonnec *et al.*, 2000). In this paper, we compare the X-ray structures of three compounds from this series, (I), (II) and (III), involving different spacer groups between the two aryl rings.



(I) X = CO
(II) X = CONH
(III) X = NHCO, H_2O

The atom-numbering schemes and molecular conformations adopted by compounds (I), (II) and (III) are depicted in Figs. 1, 2 and 3, respectively. For each compound, the pyrazolidine-3,5-dione heterocycle is almost planar; the displacement of the atoms from their mean plane does not exceed 0.096 Å. The C24 and C6 substituents deviate from this plane by distances ranging from 0.35 to 0.78 Å. In (III), the terminal part of the butyl chain and the spiropentyl groups are disordered. Two orientations were found for these moieties, with occupancy factors of 0.57 and 0.43 for C26—C27 and C26′—C27′, and 0.63 and 0.37 for C29—C30 and C29′—C30′.

The three compounds present some differences in the conformation of the Ph–X–PhCO_2H_{ortho} moiety. Indeed, the orientation of the central aryl ring (C7–C12) is quite different for (I) when compared with the other two. The N1—C6—C7—C8 torsion angles are −2.6 (3), −78.4 (3) and −98.4 (2)° for (I), (II) and (III), respectively. Furthermore, the angle between the planes of the two aryl rings varies depending on the nature of the linkage (carbonyl, amide or retroamide). In compound (I), the two rings form a dihedral angle of 82.8 (1)°, with the carbonyl function almost in the same plane as the central aryl ring [C11—C10—C34—O35 −10.5 (3)°]. In (II), the two phenyl rings are twisted slightly from coplanarity [dihedral angle between the planes 32.3 (1)°], whereas in (III), they are distorted by 88.0 (1)°. In fact, for these two latter derivatives, the amide function is in the same plane as the central aryl ring [the dihedral angle between the planes is 11.5 (5)° for (II) and 10.5 (2)° for (III)]. However, there is a difference in the orientation of the terminal phenyl ring (C13–C18) with respect to the amide function. In (II), the aryl and amide moieties are almost coplanar [dihedral angle 21.1 (4)°]. This conformation is stabilized by an intramolecular hydrogen bond between the amide and carboxylic acid moieties (N36—H36···O21; Table 2). In (III), this intramolecular hydrogen bond is not present and the terminal aryl ring is perpendicular to the retroamide group [dihedral angle 81.7 (1)°]. For all three derivatives, the carboxylic acid function is almost coplanar with the corresponding phenyl ring, with C13—C14—C19—O21 torsion angles of 3.7 (3), −12.1 (5) and

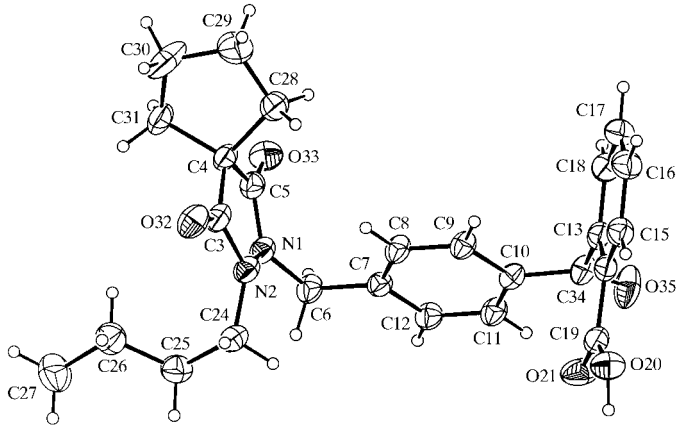


Figure 1
A view of the molecule of compound (I), with displacement ellipsoids drawn at the 30% probability level and H atoms shown as small spheres of arbitrary radii.

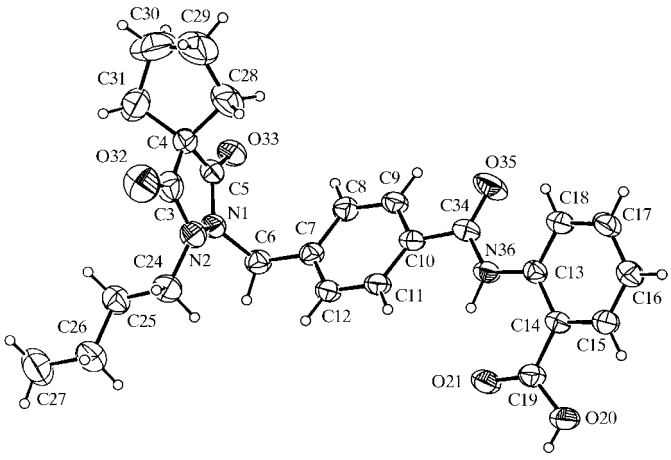


Figure 2
A view of the molecule of compound (II), with displacement ellipsoids drawn at the 30% probability level and H atoms shown as small spheres of arbitrary radii.

4.9 (3)° for (I), (II) and (III), respectively. The C14—C19 distances, ranging from 1.480 to 1.489 Å, are shorter than common single bonds, indicative of a delocalization between the two groups.

In addition to the intramolecular hydrogen bond observed in (II), some intermolecular donor–acceptor interactions are also found for the three derivatives; details of these are given in Tables 1, 2 and 3. For (I) and (II), the carboxylic acid group is involved in a hydrogen bond with the O33 acceptor atom (O20—H20···O33; Tables 1 and 2). For compound (III), the cocrystallized water molecule is involved in the hydrogen-bonding pattern. It interacts as a double H-atom donor with the pyrazolidine-3,5-dione heterocycle (O37—H37*A*···O33 and O37—H37*B*···O32; Table 3) and as an H-atom acceptor with the carboxylic acid moiety (O20—H20···O37; Table 3). Furthermore, an intermolecular hydrogen bond exists between the amide functions (N36—H36···O35; Table 3).

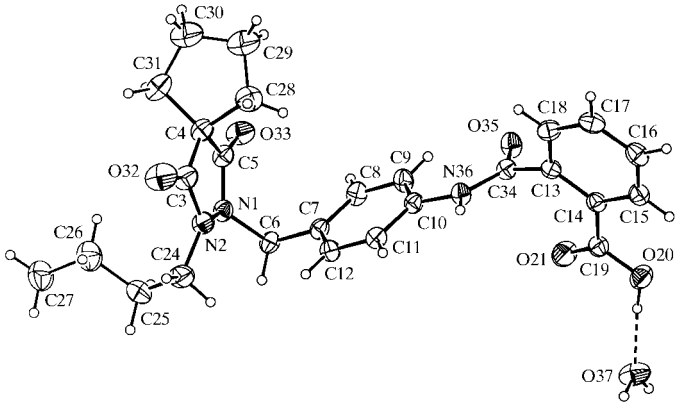


Figure 3
A view of the molecule of compound (III), with displacement ellipsoids drawn at the 30% probability level and H atoms shown as small spheres of arbitrary radii. Only one conformation of the terminal part of the alkyl chain (C26—27) and the spiropentyl group (C29—C30) is shown.

Experimental

The syntheses of compounds (I), (II) and (III) have been reported previously by Le Bourdonnec *et al.* (2000). Crystals were obtained by slow evaporation of an isooctane–ethyl acetate solution for (I), a toluene–ethyl acetate solution for (II) and an ethyl acetate solution for (III), all at room temperature.

Compound (I)

Crystal data

$C_{26}H_{28}N_2O_5$
M_r = 448.50
Triclinic, $P\overline{1}$
a = 10.530 (1) Å
b = 11.469 (1) Å
c = 11.491 (1) Å
α = 109.589 (8)°
β = 112.690 (8)°
γ = 97.640 (9)°
V = 1150.02 (18) Å^3
Z = 2
D_x = 1.295 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 40–50°
μ = 0.73 mm^{-1}
T = 293 (2) K
Block, colourless
0.31 × 0.29 × 0.23 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.804, T_{max} = 0.849
4750 measured reflections
4511 independent reflections
3537 reflections with $I > 2\sigma(I)$
R_{int} = 0.043
θ_{max} = 71.9°
$h = -12 \rightarrow 12$
$k = 0 \rightarrow 14$
$l = -14 \rightarrow 13$
3 standard reflections
every 200 reflections
frequency: 60 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.152
S = 1.04
4511 reflections
302 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0781P)^2 + 0.3037P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O20—H20···O33^{i}	0.90 (3)	1.79 (3)	2.687 (3)	174 (3)

Symmetry code: (i) $x, y-1, z$.

Compound (II)

Crystal data

$C_{26}H_{29}N_3O_5$
M_r = 463.52
Monoclinic, $P2_1/c$
a = 16.122 (1) Å
b = 12.682 (1) Å
c = 11.920 (1) Å
β = 97.139 (7)°
V = 2418.3 (3) Å^3
Z = 4
D_x = 1.273 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 40–50°
μ = 0.73 mm^{-1}
T = 293 (2) K
Platelet, colourless
0.29 × 0.10 × 0.03 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.817, T_{max} = 0.979
6842 measured reflections
4757 independent reflections
1972 reflections with $I > 2\sigma(I)$

R_{int} = 0.026
θ_{max} = 71.9°
$h = -19 \rightarrow 14$
$k = -15 \rightarrow 0$
$l = -14 \rightarrow 14$
3 standard reflections
every 200 reflections
frequency: 60 min
intensity decay: 5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.164
S = 0.96
4757 reflections
315 parameters

H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0743P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 2
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N36—H36···O21	0.95 (4)	1.86 (4)	2.686 (3)	144 (3)
O20—H20···O33^{ii}	0.83 (4)	1.79 (4)	2.611 (3)	169 (4)

Symmetry code: (ii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$.

Compound (III)

Crystal data

$C_{26}H_{29}N_3O_5 \cdot H_2O$
M_r = 481.54
Monoclinic, $P2_1/c$
a = 18.681 (1) Å
b = 9.565 (1) Å
c = 14.837 (1) Å
β = 111.904 (7)°
V = 2459.7 (3) Å^3
Z = 4

D_x = 1.300 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 40–50°
μ = 0.76 mm^{-1}
T = 293 (2) K
Platelet, colourless
0.26 × 0.11 × 0.07 mm

Table 3
Hydrogen-bonding geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
O20—H20···O37	0.95 (4)	1.70 (4)	2.623 (3)	163 (4)
O37—H37A···O33^{iii}	0.84 (4)	1.93 (4)	2.759 (3)	171 (4)
O37—H37B···O32^{iv}	0.89 (4)	1.91 (4)	2.793 (3)	174 (3)
N36—H36···O35^{v}	0.93 (3)	2.08 (3)	3.002 (2)	171 (2)

Symmetry codes: (iii) $1-x, 2-y, -z$; (iv) $1-x, 1-y, -z$; (v) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$.

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.826, T_{max} = 0.948
6162 measured reflections
4835 independent reflections
3166 reflections with $I > 2\sigma(I)$

R_{int} = 0.013
θ_{max} = 71.9°
$h = -23 \rightarrow 21$
$k = -7 \rightarrow 11$
$l = 0 \rightarrow 18$
3 standard reflections
every 200 reflections
frequency: 60 min
intensity decay: 4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.151
S = 1.02
4835 reflections
333 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0704P)^2 + 0.7853P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.008
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0016 (2)

H atoms attached to C atoms were treated as riding using *SHELXL*97 (Sheldrick, 1997) defaults, whereas the H atoms of the N—H and O—H groups were refined on position and with isotropic displacement parameters.

For all compounds, data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1992); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *PLATON* (Spek, 2000); program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON*; software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1071). Services for accessing these data are described at the back of the journal.

References

Altomare, A., Burla, M. C., Camalli, M., Cascarano, G., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.
Enraf–Nonius (1992). *CAD*-4 *EXPRESS*. Enraf–Nonius, Delft, The Netherlands.
Le Bourdonnec, B., Meulon, E., Yous, S., Goossens, J.-F., Houssin, R. & Hénichart, J.-P. (2000). *J. Med. Chem.* **43**, 2685–2697.
North, A. C. T., Phillips, D. C. & Mathews, F. S.(1968). *Acta Cryst.* A**24**, 351–359.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2000). *PLATON*. University of Utrecht, The Netherlands.
Wexler, R. R., Greenlee, W. J., Irvin, J. D., Goldberg, M. R., Prendergast, K., Smith, R. D. & Timmermans, P. B. M. W. (1996). *J. Med. Chem.* **39**, 625–656.