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Novel selective κ-opioid ligands

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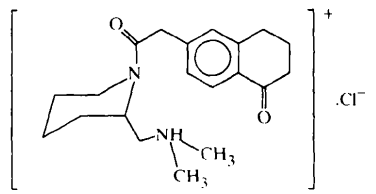
Abstract

The single-crystal X-ray structures of (−)-dimethyl[(2*S*)-1-(5,6,7,8-tetrahydro-5-oxonaphthalene-2-acetyl)piperidin-2-ylmethyl]ammonium chloride, $C_{20}H_{29}N_2O_2^+\cdot Cl^-$ (BRL-53001A), and (−)-ethylmethyl[(2*S*)-1-(5,6,7,8-tetrahydro-5-oxonaphthalene-2-acetyl)piperidin-2-ylmethyl]-ammonium chloride dihydrate, $C_{21}H_{31}N_2O_2^+\cdot Cl^-\cdot 2H_2O$ (BRL-53188A), have been determined. The two molecules have different conformations in the 1-tetralon-6-ylacetyl residue but the same conformation in the 1-acetyl-2-(dialkylaminomethyl)piperidine moiety. The conformations found are in agreement with the required chemical features for κ affinity and antinociceptive potency.

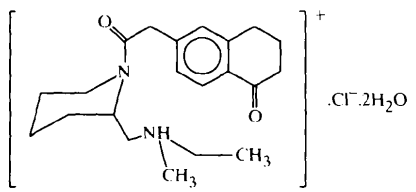
Comment

Selective κ-opioid agonists may have therapeutic utility as analgesics lacking the adverse side effects associated with morphine and other current opioid therapies (Millan, 1990). However, κ-agonists produce a variety of side effects, *e.g.* diuresis, sedation and possibly dysphoria (Rees, 1992). In order to obtain novel κ-agonists with safer biological profiles, Giardina *et al.* (1994) incorporated novel acyl groups in the 2-(1-pyrrolidinylmethyl)piperidine framework, which is the diamine counterpart of the potent and κ-selective antinociceptive agents 1-{(2*S*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl}pyrrolidinium chloride monohydrate (BRL-52537A) and 1-{(2*S*)-1-[(4-trifluorophenyl)acetyl]piperidin-2-ylmethyl}pyrrolidinium chloride (BRL-52656A). Furthermore, to optimize the biological profile they incorporated in the basic side chain a variety of linear and branched amines.

We report here the crystal structures of two compounds of this series, namely, (−)-dimethyl[(2*S*)-1-(5,6,7,8-tetrahydro-5-oxonaphthalene-2-acetyl)piperidin-2-ylmethyl]ammonium chloride (BRL-53001A) and (−)-ethylmethyl[(2*S*)-1-(5,6,7,8-tetrahydro-5-oxonaphthalene-2-acetyl)piperidin-2-ylmethyl]ammonium chloride dihydrate (BRL-53188A). The two molecules differ by one methylene group in one of the amine substituents. In the crystal, both molecules have the same conformation for the 1-acetyl-2-(dialkylaminomethyl)piperidine residue [an r.m.s. fit (Hypercube, 1993) gives a deviation of 0.114 Å for that part of the molecule] but a different conformation for the 5,6,7,8-tetrahydro-5-oxonaphthylene-2-acetyl moiety. The C4—C7—C8—N10 torsion angle is antiperiplanar in BRL-53001A and (+)-synclinal in BRL-53888A. Furthermore, the C3—C4—C7—C8 torsion angles are −93.3 (3) and 18.3 (6)° in BRL-53001A and BRL-53888A, respectively. The periplanar conformation in BRL-53888A causes the C4—C7—C8 angle to open to a value of 115.7 (4)°. Although the conformations are different, the least-squares planes through the phenyl and amide moieties are perpendicular in both cases [96.8 (1) and 91.5 (2)° for BRL-53001A and BRL-53888A, respectively]. The puckering parameters of the piperidinyl rings (sequence N10—C11—C12—C13—C14—C15) indicate a $^4C_1$ conformation slightly flattened towards an E_3 conformation. The flattening causes enlarged C13—C14—C15 angles. In both structures, the aminomethyl substituent adopts an axial position and is in a *syn* conformation with respect to the carbonyl-O atom. The pharmacophore dihedral angle, Nsp^2—C—C—N, common to most κ-opioid agonists, is 58.1 (3) and 56.7 (5)° in BRL-53001A and BRL-53888A, respectively.



BRL-53001A



BRL-53888A

Almost identical conformations were found in the crystal structures of two 1-(arylacetyl)-2-(aminomethyl)-piperidine derivatives (Peeters *et al.*, 1999). In both structures, the Cl^- anion is hydrogen bonded to N17. In BRL-53888A, the Cl^- anion is further hydrogen bonded to the H_2O molecules forming a two-dimensional network with infinite chains in the *a* and *b* directions. A conformational search (Hypercube, 1993) starting from the crystal structure molecular geometry of BRL-53001A, with random variation of the dihedral angles C3—C4—C7—C8 (τ_1), C4—C7—C8—N10 (τ_2), N10—C15—C16—N17 (τ_3) and C15—C16—N17—H17 (τ_4), and geometry optimization within

0.01 kcal mol^{-1} (1 kcal mol^{-1} = 4.1868 kJ mol^{-1}) using the *HyperMM*$^{+}$ program (Hypercube, 1994), revealed that eight of the ten low-energy conformations ($E - E_{min} < 2$ kcal mol^{-1}) adopt a (+)-synclinal conformation for τ_3. The two remaining low-energy conformations adopt an antiperiplanar conformation for this torsion angle. The conformational potential-energy surfaces calculated as a function of the pairs of torsion angles $\tau_1\tau_2$ and $\tau_3\tau_4$ (two-dimensional 10° grid search; restrained energy minimization within 0.25 kcal mol^{-1}) are shown in Figs. 3 and 4, respectively. The conformations found in the crystal structures of seven members of the series (this paper; Peeters *et al.*, 1998; Peeters, 1999) correspond roughly to four of the six low-energy regions of the $\tau_1\tau_2$ surface. In the $\tau_3\tau_4$ surface, these conformations are all clustered together in the 60/–60° region. These results indicate severely restricted rotation about

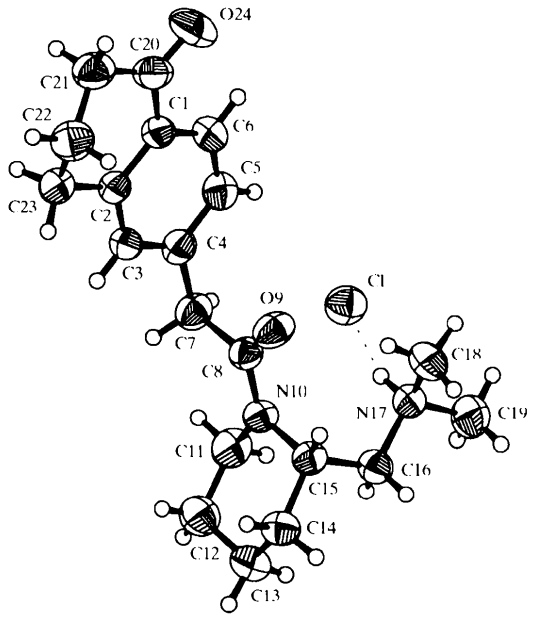


Fig. 1. View of compound BRL-53001A with atom labels. Displacement ellipsoids are drawn at the 50% probability level.

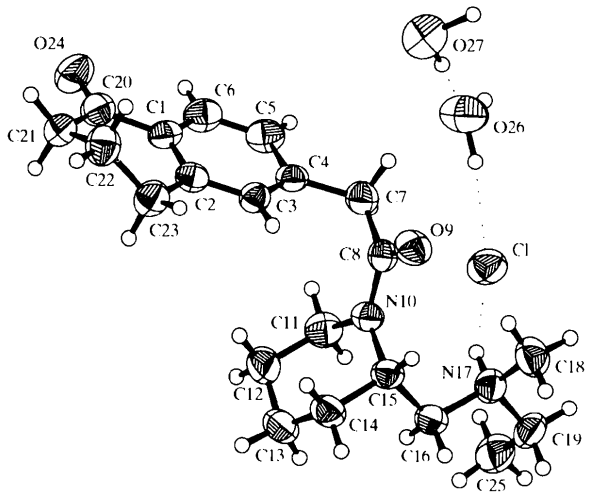


Fig. 2. View of compound BRL-53888A with atom labels. Displacement ellipsoids are drawn at the 50% probability level.

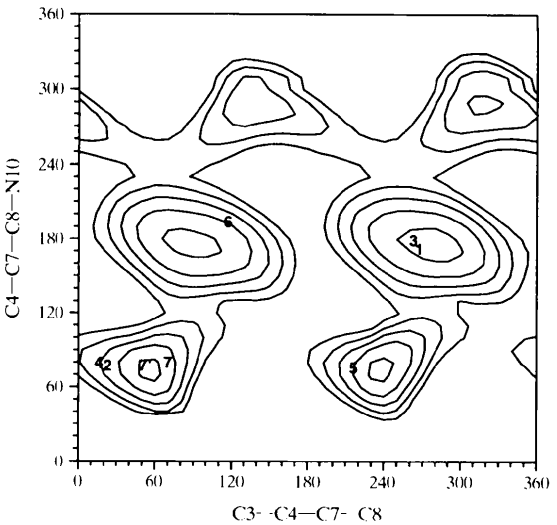


Fig. 3. Conformational potential energy surface for BRL-53001A. The outermost contour is 19 kcal mol^{-1} and the contour interval is 1 kcal mol^{-1}. The numbers refer to the crystal structure conformations of (1) BRL-53001A, (2) BRL-53188A, (3) BRL-52536A [(+)-1-{(2*R*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl}-pyrrolidinium chloride monohydrate], (4) BRL-52781A [(−)-1-{(2*S*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl}piperidinium chloride], (5) BRL-52656A, (6) BRL-52627A [dimethyl-{(2*S*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylethyl}ammonium chloride monohydrate], and (7) and (7′) BRL-52538A [dimethyl-{(2*S*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl}ammonium chloride hemihydrate].

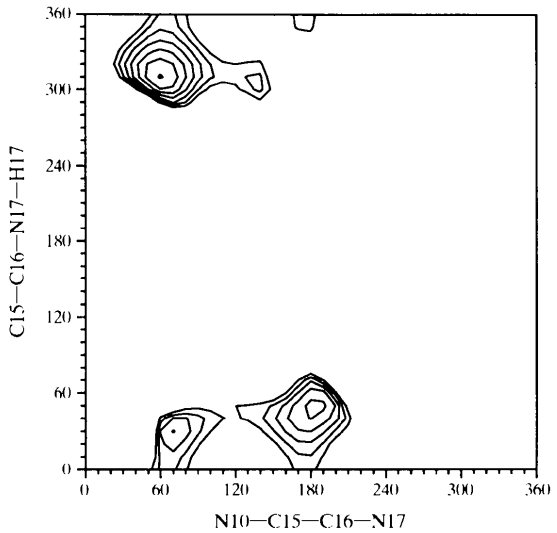


Fig. 4. Conformational potential energy surface for compound BRL-53888A. The outermost contour is 19 kcal mol^{-1} and the contour interval is 1 kcal mol^{-1}.

the C15—C16 and C16—N17 bonds, with the global minimum at the pharmacophore dihedral angle τ_3 = 60°. Such a conformation is required for κ affinity and antinociceptive potency (Vecchietti *et al.*, 1991).

Experimental

Samples of the title compounds were gifts from SmithKline Beecham Pharmaceuticals. Their syntheses are described by Giardina *et al.* (1994). The crystals of BRL-53001A and BRL-53888A used in the diffraction experiment were obtained by slow evaporation at room temperature from methanol/methyl isobutyl ketone and methanol/ethyl acetate solutions, respectively.

BRL-53001A

Crystal data

$C_{20}H_{29}N_2O_2^+\cdot Cl^-$
M_r = 364.90
Orthorhombic
$P2_12_12_1$
a = 7.3648 (5) Å
b = 8.1825 (6) Å
c = 32.657 (2) Å
V = 1968.0 (2) Å^3
Z = 4
D_x = 1.232 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 42 reflections
θ = 10.95–27.70°
μ = 1.830 mm^{-1}
T = 293 K
Plate
0.44 × 0.17 × 0.04 mm
Colourless

Data collection

Siemens $P4$ four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (*XEMP*; Siemens, 1989)
T_{min} = 0.565, T_{max} = 0.929
2857 measured reflections
2603 independent reflections
2418 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.022
θ_{max} = 69.09°
$h = -1 \rightarrow 8$
$k = -1 \rightarrow 8$
$l = -1 \rightarrow 39$
3 standard reflections every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.121
S = 1.136
2603 reflections
229 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0656P)^2 + 0.3139P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0051 (5)
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)
Absolute structure: Flack (1983)
Flack parameter = 0.00 (2)

Table 1. *Selected torsion angles (°) for BRL-53001A*

C3—C4—C7—C8	−93.3 (3)	C13—C14—C15—C16	−73.8 (3)
C4—C7—C8—N10	173.1 (2)	N10—C15—C16—N17	58.1 (3)
O9—C8—N10—C15	0.9 (4)	C15—C16—N17—H17	−59.3

Table 2. *Hydrogen-bonding geometry (Å, °) for BRL-53001A*

D—H···A	D—H	H···A	D···A	D—H···A
N17—H17···Cl	0.91	2.23	3.094 (3)	159

BRL-53888A

Crystal data

$C_{21}H_{31}N_2O_2^+\cdot Cl^-\cdot 2H_2O$
M_r = 414.96
Orthorhombic
$P2_12_12_1$
a = 7.2011 (8) Å
b = 7.6300 (6) Å
c = 41.223 (3) Å
V = 2265.0 (3) Å^3
Z = 4
D_x = 1.217 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 37 reflections
θ = 2.29–16.50°
μ = 1.720 mm^{-1}
T = 293 K
Plate
0.24 × 0.14 × 0.04 mm
Colourless

Data collection

Siemens $P4$ four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (*XEMP*; Siemens, 1989)
T_{min} = 0.800, T_{max} = 0.934
3227 measured reflections
2928 independent reflections
2087 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.022
θ_{max} = 69.09°
$h = -1 \rightarrow 7$
$k = -9 \rightarrow 1$
$l = -1 \rightarrow 49$
3 standard reflections every 100 reflections
intensity decay: 4.0%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.130
S = 1.062
2928 reflections
256 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0491P)^2 + 1.0035P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0028 (3)
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)
Absolute structure: Flack (1983)
Flack parameter = 0.01 (3)

Table 3. *Selected torsion angles (°) for BRL-53888A*

C3—C4—C7—C8	18.3 (6)	C13—C14—C15—C16	−71.6 (5)
C4—C7—C8—N10	78.7 (5)	N10—C15—C16—N17	56.7 (5)
O9—C8—N10—C15	0.5 (6)	C15—C16—N17—H17	−59.0

Table 4. *Hydrogen-bonding geometry (Å, °) for BRL-53888A*

D—H···A	D—H	H···A	D···A	D—H···A
N17—H17···Cl	0.91	2.28	3.129 (4)	156
O26—H261···Cl	1.00	2.19	3.187 (4)	172
O27—H272···O26	1.14	1.63	2.762 (5)	171
O26—H262···Cl^{i}	0.82	2.40	3.219 (4)	177
O27—H271···Cl^{ii}	1.22	2.07	3.262 (4)	164

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

The structures were solved by direct methods and refined by full-matrix least squares for all reflections. H atoms were placed geometrically (except those of the H_2O molecules in BRL-53888A, which were obtained from a difference Fourier synthesis) and refined with a riding model and with U_{iso} constrained to be $1.25U_{eq}$ of the parent atom.

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structures: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structures: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *DIAMOND* (Bergerhoff, 1996); software used to prepare material for publication: *PARST* (Nardelli, 1983).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1280). Services for accessing these data are described at the back of the journal.

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4-Ethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide and 4-ethyl-2,3-dihydro-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide†

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Abstract

A series of 4*H*-1,2,4-pyridothiadiazine 1,1-dioxides and 2,3-dihydro-4*H*-1,2,4-pyridothiadiazine 1,1-dioxides were tested as possible allosteric modulators of the (*R/S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid receptors; the most active is 4-ethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide, $C_8H_{11}N_3O_2S$. Its crystal molecular geometry is compared with that of the -pyrido[4,3-*e*]- compound, $C_8H_{11}N_3O_2S$, a less potent analogue.

Comment

A series of 4*H*- and 2,3-dihydro-4*H*-1,2,4-pyridothiadiazine 1,1-dioxides, belonging to three different chemical classes (as a function of the N-atom position in the heterocycle) and bearing various alkyl and aryl substituents at the 2, 3 and 4 positions, were synthesized and tested as possible allosteric modulators of the (*R/S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid (AMPA) receptors. Many compounds were found to be more potent than the reference compounds diazoxide (Bandoli & Nicolini, 1977) and aniracetam as potentiators of the AMPA current in rat cortex mRNA-injected *Xenopus* oocytes. The most active compound, 4-ethyl-2,3-dihydro-4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide, (1), revealed an *in vitro* activity not far from that of cyclothiazide, the most potent allosteric modulator of AMPA receptors reported to date. Structure–activity relationships were deduced and indicated the possible dissociation between the structure requirements leading to a biological activity

† Systematic names: 4-ethyl-3,4-dihydro-2*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide and 4-ethyl-3,4-dihydro-2*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide.