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concluded from computational studies and <sup>1</sup>H NMR spectroscopic analysis (Vecchiotti *et al.*, 1991) that the pharmacophore N—C—C—N<sub>sp<sup>2</sup></sub> torsion angle should be *ca* 60° in a low energy conformation. In order to confirm these results the crystal structures of two members of the series were determined, namely, (+)-1-[(2*R*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl]pyrrolidinium chloride monohydrate (BRL-52536A) and (–)-1-[(2*S*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl]piperidinium chloride (BRL-52781A).

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## Two 1-(Arylacetyl)-2-(aminomethyl)-piperidine Derivatives, a Novel Class of Highly Selective $\kappa$ -Opioid Analgesics

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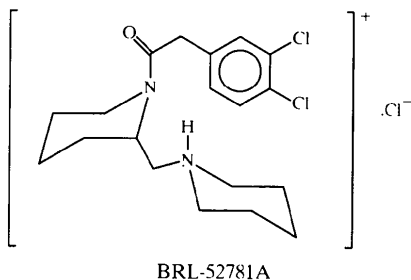
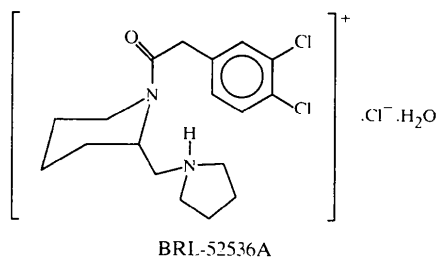
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### Abstract

The single-crystal X-ray structures of (+)-1-[(2*R*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl]-pyrrolidinium chloride monohydrate (C<sub>18</sub>H<sub>25</sub>Cl<sub>2</sub>N<sub>3</sub>O<sup>+</sup>·Cl<sup>−</sup>·H<sub>2</sub>O; BRL-52536A) and (–)-1-[(2*S*)-1-[(3,4-dichlorophenyl)acetyl]piperidin-2-ylmethyl]piperidinium chloride (C<sub>19</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>2</sub>O<sup>+</sup>·Cl<sup>−</sup>; BRL-52781A) have been determined. BRL-52536A is the inactive stereoisomer of BRL-52537A, the highly selective and potent lead compound of the series. The pharmacophore N—C—C—N<sub>sp<sup>2</sup></sub> torsion angle is (+)-synclinal in the 2*S* configuration.

### Comment

Over the last decade,  $\kappa$ -opioid agonists have received increased interest as possible safe and effective analgesics for the treatment of acute and chronic pain (Rees, 1992). Vecchiotti *et al.* (1991) described the synthesis and structure–activity relationships as  $\kappa$ -opioid analgesics of a novel class of 1-(arylacetyl)-2-(aminomethyl)piperidine derivatives. Antinociceptive activity and  $\kappa$  affinity were found to be extremely enantiospecific since only compounds with the 2*S* configuration displayed significant activity. Furthermore, it was



The bond lengths do not display outstanding features. The internal angles of the phenyl ring reflect the substitution pattern (Domenicano & Murray-Rust, 1979). The piperidine ring has a chair conformation slightly flattened towards an envelope conformation, with the flap at C12, resulting in an enlarged C13—C14—C15 angle. The 2-substituent is in an axial position and in a *syn* conformation with respect to the carbonyl O atom. The global conformation of the molecules is further determined by the torsion angles C3—C4—C7—C8, C4—C7—C8—N10, N10—C15—C16—N17 and C15—C16—N17—H17. In both crystal structures, the pharmacophore N10—C15—C16—N17 torsion angle and the C15—C16—N17—H17 torsion angle are synclinal, confirming the computational results. The observed conformation is probably a result of the electronic attraction between the charged N atom and the carbonyl group. The dihedral angle between the least-squares planes of the phenyl and amido groups is 101.0 (1) and 97.1 (1)° in BRL-52536A and BRL-52781A, respectively, indicating perpendicularity of the two planes. In both structures, the Cl<sup>−</sup> anion is hydrogen bonded to N17 [N17···Cl 3.098 (3) and 3.097 (2), H17···Cl 2.22 and 2.21 Å, and N17—H17···Cl 162 and 166°, for BRL-52536A and BRL-

52781A, respectively]. In BRL-52536A, the Cl<sup>-</sup> anion is also hydrogen bonded to the H<sub>2</sub>O molecule [O...Cl 3.137 (3), H1O...Cl 2.32 Å and O—H1O...Cl 137°].

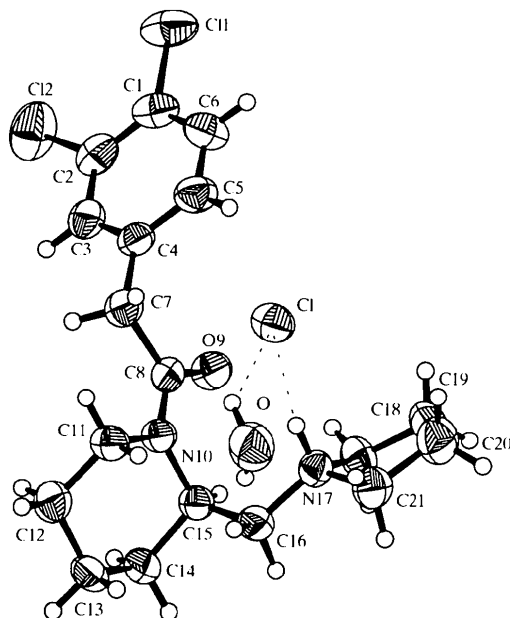


Fig. 1. View of BRL-52536A with atom labels. Displacement ellipsoids are drawn at the 50% probability level.

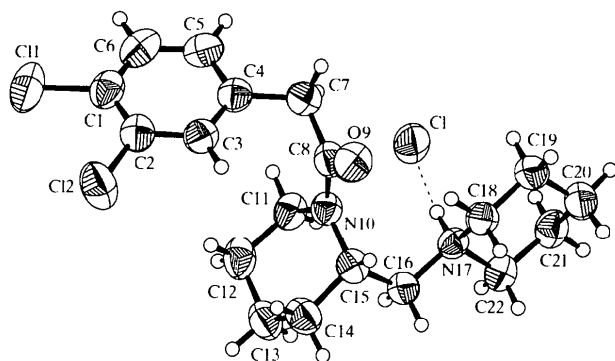


Fig. 2. View of BRL-52781A with atom labels. Displacement ellipsoids are drawn at the 50% probability level.

## Experimental

Samples of the title compounds were gifts from SmithKline Beecham Pharmaceuticals. The syntheses have been described by Vecchietti *et al.* (1991). The crystals used in the diffraction experiments were obtained by slow evaporation at room temperature from methanol–ethyl acetate solutions.

### BRL-52536A

#### Crystal data

C<sub>18</sub>H<sub>25</sub>Cl<sub>2</sub>N<sub>2</sub>O<sup>+</sup>.Cl<sup>-</sup>.H<sub>2</sub>O  
M<sub>r</sub> = 409.77

Cu Kα radiation  
λ = 1.54184 Å

#### Monoclinic

*P*2<sub>1</sub>  
a = 6.8417 (4) Å  
b = 10.2086 (5) Å  
c = 14.6099 (8) Å  
β = 101.574 (5)°  
V = 999.67 (9) Å<sup>3</sup>  
Z = 2  
D<sub>x</sub> = 1.361 Mg m<sup>-3</sup>  
D<sub>m</sub> not measured

#### Data collection

Siemens P4 four-circle diffractometer  
ω/2θ scans  
Absorption correction: ψ scan (XEMP; Siemens, 1989)  
T<sub>min</sub> = 0.320, T<sub>max</sub> = 0.653  
2603 measured reflections  
2034 independent reflections

#### Refinement

Refinement on F<sup>2</sup>  
R[F<sup>2</sup> > 2σ(F<sup>2</sup>)] = 0.036  
wR(F<sup>2</sup>) = 0.103  
S = 1.041  
2034 reflections  
227 parameters  
H atoms constrained  
w = 1/[σ<sup>2</sup>(F<sub>o</sub><sup>2</sup>) + (0.0540P)<sup>2</sup> + 0.2242P]  
where P = (F<sub>o</sub><sup>2</sup> + 2F<sub>c</sub><sup>2</sup>)/3  
(Δ/σ)<sub>max</sub> = 0.001  
Δρ<sub>max</sub> = 0.28 e Å<sup>-3</sup>  
Δρ<sub>min</sub> = -0.25 e Å<sup>-3</sup>

Cell parameters from 39 reflections  
θ = 10.70–27.89°  
μ = 4.260 mm<sup>-1</sup>  
T = 293 K  
Block  
0.45 × 0.15 × 0.10 mm  
Colourless

1941 reflections with F<sup>2</sup> > 2σ(F<sup>2</sup>)  
R<sub>int</sub> = 0.049  
θ<sub>max</sub> = 67.46°  
h = -1 → 8  
k = -1 → 12  
l = -17 → 17  
3 standard reflections every 100 reflections  
intensity decay: none

Extinction correction: SHELXL93 (Sheldrick, 1993)  
Extinction coefficient: 0.0051 (9)  
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-52536A

C3—C4—C7—C8	101.3 (4)	C13—C14—C15—C16	76.1 (4)
C4—C7—C8—N10	-179.4 (3)	N10—C15—C16—N17	-63.5 (4)
O9—C8—N10—C15	-3.9 (5)	C15—C16—N17—H17	57.6

### BRL-52781A

#### Crystal data

C<sub>19</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>2</sub>O<sup>+</sup>.Cl<sup>-</sup>  
M<sub>r</sub> = 405.77  
Orthorhombic  
*P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>  
a = 7.0585 (6) Å  
b = 7.0673 (4) Å  
c = 40.530 (2) Å  
V = 2021.8 (2) Å<sup>3</sup>  
Z = 4  
D<sub>x</sub> = 1.333 Mg m<sup>-3</sup>  
D<sub>m</sub> = 1.348 Mg m<sup>-3</sup>  
D<sub>m</sub> measured by flotation in *n*-heptane/CCl<sub>4</sub>

Cu Kα radiation  
λ = 1.54184 Å  
Cell parameters from 42 reflections  
θ = 11.76–27.98°  
μ = 4.170 mm<sup>-1</sup>  
T = 293 K  
Block  
0.40 × 0.24 × 0.20 mm  
Colourless

#### Data collection

Siemens P4 four-circle diffractometer

2065 reflections with F<sup>2</sup> > 2σ(F<sup>2</sup>)

$\omega/2\theta$  scans  
 Absorption correction:  
 $\psi$  scan (XEMP; Siemens,  
 1989)  
 $T_{\min} = 0.153$ ,  $T_{\max} = 0.434$   
 3011 measured reflections  
 2162 independent reflections

$R_{\text{int}} = 0.023$   
 $\theta_{\max} = 69.41^\circ$   
 $h = -1 \rightarrow 8$   
 $k = -1 \rightarrow 7$   
 $l = -1 \rightarrow 49$   
 3 standard reflections  
 every 100 reflections  
 intensity decay: none

### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.032$   
 $wR(F^2) = 0.097$   
 $S = 1.059$   
 2721 reflections  
 227 parameters  
 H atoms constrained  
 $w = 1/[\sigma^2(F_o^2) + (0.0492P)^2 + 0.3240P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} = 0.001$   
 $\Delta\rho_{\max} = 0.15 \text{ e } \text{\AA}^{-3}$   
 $\Delta\rho_{\min} = -0.14 \text{ e } \text{\AA}^{-3}$

Extinction correction:  
 SHELXL93 (Sheldrick,  
 1993)  
 Extinction coefficient:  
 0.0041 (3)  
 Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)  
 Absolute structure:  
 Flack (1983)  
 Flack parameter =  $-0.03$  (2)

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## (4-Methoxyphenyl)diphenylmethanol, an Unusual Tetramer Containing a D[R] Pattern of Hydrogen Bonds, and Tris(2-methoxyphenyl)methanol

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Table 2. Selected torsion angles ( $^\circ$ ) for BRL-52781A

C3—C4—C7—C8	15.9 (4)	C13—C14—C15—C16	-73.7 (3)
C4—C7—C8—N10	77.2 (3)	N10—C15—C16—N17	53.4 (3)
O9—C8—N10—C15	-1.3 (4)	C15—C16—N17—H17	-65.9

The title structures were solved by direct methods and refined by full-matrix least squares on  $F^2$  for all reflections. H atoms were placed geometrically, and refined with a riding model and with  $U_{\text{iso}}$  constrained to be  $1.25U_{\text{eq}}$  of the carrier atom.

For both compounds, data collection: XSCANS (Siemens, 1996); cell refinement: XSCANS; data reduction: XSCANS; program(s) used to solve structures: SIR92 (Altomare *et al.*, 1994); program(s) used to refine structures: SHELXL93 (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: NA1373). Services for accessing these data are described at the back of the journal.

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### Abstract

(4-Methoxyphenyl)diphenylmethanol (C<sub>20</sub>H<sub>18</sub>O<sub>2</sub>) crystallizes with two independent molecules; the molecules are linked by O—H···O hydrogen bonds into centrosymmetric tetramers in which two molecules form a cyclic R<sub>3</sub><sup>2</sup>(16) motif from which the other two are pendant, giving a D<sub>3</sub><sup>3</sup>(11)[R<sub>2</sub><sup>2</sup>(16)] pattern. In tris(2-methoxyphenyl)methanol (C<sub>22</sub>H<sub>22</sub>O<sub>4</sub>) the hydroxy H atoms are disordered over two sites; whichever site is occupied, an intramolecular O—H···O hydrogen bond is formed with a methoxy O atom.

### Comment

Triphenylmethanol, Ph<sub>3</sub>COH, crystallizes as almost perfectly tetrahedral tetramers (Ferguson *et al.*, 1992), in which the four hydroxy-H atoms are mobile over 12 sites along the six O···O edges of the tetrahedron (Aliev *et al.*, 1998). By contrast, tris(4-methoxyphenyl)methanol [(4-MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>COH] forms an open dimer in which only one of the two independent hydroxy groups is involved in hydrogen bonding (Ferguson *et al.*, 1996). In view of the major differences in supramolecular aggregation between Ph<sub>3</sub>COH and (4-MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>COH, we have now investigated the structures of (I) (4-methoxyphenyl)diphenylmethanol [(4-MeOC<sub>6</sub>H<sub>4</sub>)Ph<sub>2</sub>COH] and (II) tris(2-methoxyphenyl)methanol [(2-MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>COH].