Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Twinned 1-{2-[bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenyl)propyl)piperazinium chloride (GBR12909)

Judith L. Flippen-Anderson,[a]* Jeffrey R Deschamps,[a] Clifford George,[a] John E. Folk,[b] Arthur E. Jacobson[b] and Kenner C. Rice[b]

[a]Laboratory for the Structure of Matter, Code 6030, Naval Research Laboratory, Washington, DC 20375, USA, and [b]Laboratory of Medicinal Chemistry, Building 8, Room B1-23, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 8 Center Drive MSC 0815, Bethesda, MD 20892, USA

Correspondence e-mail: flippen@harker.nrl.navy.mil

Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.008 Å
R factor = 0.065
wR factor = 0.190
Data-to-parameter ratio = 14.2

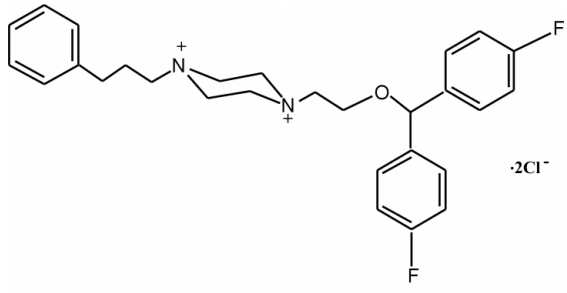
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 21 November 2001
Accepted 12 December 2001
Online 22 December 2001

GBR12909, $C_{28}H_{34}F_2N_2O$, is one of the earliest agents found to have high affinity and selectivity for the dopamine transporter (DAT). The triclinic crystal, of the hydrochloride salt of GBR12909, $C_{28}H_{34}F_2N_2O^{2+}\cdot 2Cl^-$, exhibited non-merohedral twinning.

Comment

Cocaine is one of the most widely abused drugs in the world. The reinforcing and locomotor stimulating properties of cocaine are said to be mainly mediated by the binding of cocaine to the dopamine transporter (DAT) and subsequent blockade of dopamine re-uptake into presynaptic terminals, resulting in increased neurotransmission in the mesolimbic dopaminergic system (Kuhar *et al.*, 1991; Rothman *et al.*, 1989). Studies have been aimed at the discovery and development of potent and selective DAT ligands, (Zhang *et al.*, 2000; Newman *et al.*, 1994) that may reduce the effects of cocaine and, therefore, could be used for the treatment of cocaine abuse (Glowa *et al.*, 1995*a*,*b*). GBR12909, (I), a potent if not overly selective DAT ligand, is now being examined in man for its toxicity and efficacy prior to exploration of its potential as a cocaine-treatment agent. The X-ray structure of GBR12909 will provide some of the necessary information for structure–activity studies that might lead to a new generation of more potent and selective cocaine-treatment agents.



(I)

GBR12909 hydrochloride crystallizes with two molecules per asymmetric unit. The two independent molecules are almost identical, the only difference being the relative twist of the two fluorophenyl groups (Fig. 1). The difference between the C1*B*—C10—C1*A*—C2*A* torsion angle and the corresponding torsion in the second molecule in the asymmetric unit is approximately 16°. The central six-membered ring has a normal chair conformation. Both N atoms in the ring are positively charged and hydrogen bond to a Cl ion (see Table 1). There are no other intermolecular interactions. Both aromatic moieties are extended away from the central ring and from

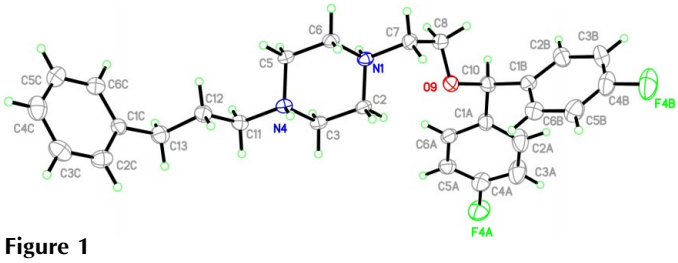


Figure 1
View of GBR12909 with 20% probability ellipsoids, showing one of the two independent molecules in the asymmetric unit.

each other. The 4-fluorophenyl rings are approximately perpendicular to one another (angle between the ring planes of 88.5 (1) and 88.6 (2)° for the two independent molecules). The third aromatic ring is approximately perpendicular to the plane formed by N4, C11, C12 and C13 [82.3 (3) and 82.2 (2)° for the two independent molecules].

Experimental

The sample of GBR12909 hydrochloride was obtained from the National Institutes of Health. Crystals were grown at NRL by slow evaporation from a mixture of 2-propanol and ethyl acetate.

Crystal data

$C_{28}H_{34}F_2N_2O^{2+}\cdot 2Cl^-$
M_r = 523.47
Triclinic, $P\overline{1}$
a = 8.5449 (4) Å
b = 14.3779 (7) Å
c = 23.2700 (12) Å
α = 83.131 (3)°
β = 80.554 (3)°
γ = 89.963 (3)°
V = 2799.4 (2) Å^3
Z = 4
D_x = 1.242 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 5787 reflections
θ = 3.1–61.4°
μ = 2.38 mm^{-1}
T = 293 (2) K
Plate, colorless
0.40 × 0.35 × 0.02 mm

Data collection

Bruker SMART 6000 diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2001)
T_{min} = 0.386, T_{max} = 0.953
9044 measured reflections
9044 independent reflections
6598 reflections with $I > 2\sigma(I)$
θ_{max} = 67.2°
$h = -10 \rightarrow 10$
$k = -16 \rightarrow 14$
$l = -26 \rightarrow 25$
56 standard reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.065
$wR(F^2)$ = 0.190
S = 0.97
9044 reflections
635 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.128P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.047
$\Delta\rho_{max}$ = 0.42 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0015 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···Cl4	0.91	2.14	3.034 (3)	166
N4—H4A···Cl3	0.91	2.11	3.012 (3)	174
N1′—H1′A···Cl2	0.91	2.13	3.027 (3)	167
N4′—H4′A···Cl1	0.91	2.11	3.018 (3)	173

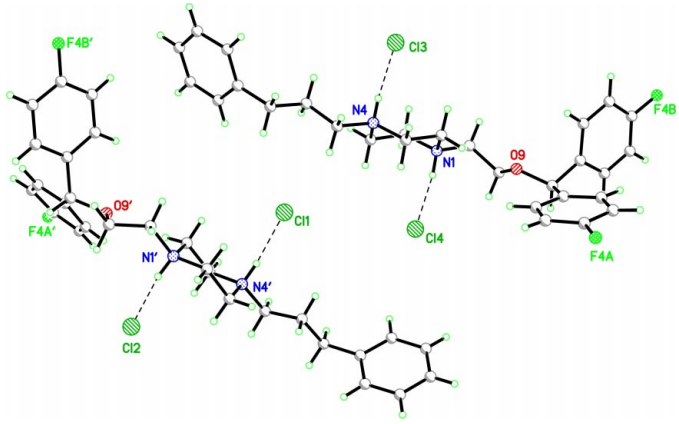


Figure 2
The asymmetric unit, showing each independent molecule hydrogen bonded to two Cl atoms.

The GBR12909 hydrochloride crystals exhibited non-merohedral twinning. Program *ROTAX*, found in the *CRYSTALS* (Watkin, 2001) suite of programs was used to determine the twin law (−1,0,0/0,1,0/0,0.4,−1). Program *ROTWIN* (Young, 2001) was used to generate a new reflection file for refinement with *SHELXTL* (Bruker, 2001). Without twinning the refinement converged to an R factor of 0.094. Adding the single twin reduced the R factor to 0.065.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1997); program(s) used to refine structure: *SHELXTL* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2001); software used to prepare material for publication: *SHELXTL* (Bruker, 2001).

The NRL authors wish to acknowledge financial support from the Office of Naval Research, Mechanics Division and the National Institute on Drug Abuse. We would also like to acknowledge the helpful discussions and interactions with Simon Parsons, Richard Cooper and Victor Young at the Workshop on Twinning preceding ECM 20 in Krakow, August 2001.

References

Bruker (2001). *SMART* (Version 5.624) and SAINT (Version 6.04) for Windows NT, *SADABS* (Version 2.03) and *SHELXTL* (Version 5.10) for UNIX. Bruker AXS Inc., Madison, Wisconsin, USA.
Glowa, J. R., Wojnicki, F. H. E., Matecka, D., Rice, K. C. & Rothman, R. B. (1995*a*). *Exp. Clin. Psychopharmacol.* **3**, 219–231.
Glowa, J. R., Wojnicki, F. H. E., Matecka, D., Rice, K. C. & Rothman, R. B. (1995*b*). *Exp. Clin. Psychopharmacol.* **3**, 232–239.
Kuhar, M. J., Ritz, M. C. & Boja, J. W. (1991). *Trends Neurosci.* **14**, 299–302.
Newman, A. H., Allen, A. C., Izenwasser, S. & Katz, J. L. (1994). *J. Med. Chem.* **37**, 2258–2261.
Rothman, R. B., Mele, A., Reid, A. A., Akunne, H., Greig, N., Thurkauf, A., Rice, K. C. & Pert, A. (1989). *FEBS Lett.* **257**, 341–344.
Sheldrick, G. M. (1997). *SHELXTL*. Version 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Watkin, D. J., Prout, C. K., Carruthers, J. R., Betheridge, P. W. & Cooper, R. I. (2001). *CRYSTALS*. Issue 11.6. Chemical Crystallography Laboratory, University of Oxford, England.
Young, V. (2001). Private Communication.
Zhang, Y., Rothman, R. B., Dersch, C. M., de Costa, B. R., Jacobson, A. E. & Rice, K. C. (2000). *J. Med. Chem.* **43**, 4840–4849.