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(+)-(3*S*,4*R*)-Norcisapride hydrogen (2*R*,3*R*)-tartrate monohydrate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.037
wR factor = 0.107
Data-to-parameter ratio = 8.0

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

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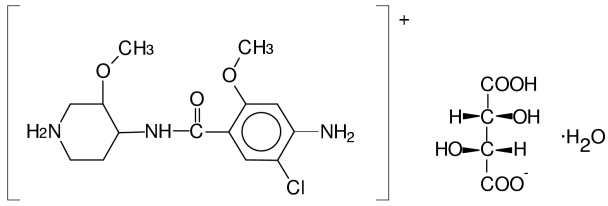
The title compound, (+)-(3*S*,4*R*)-*cis*-4-amino-5-chloro-2-methoxy-*N*-(3-methoxypiperidin-1-ium-4-yl)benzamide hydrogen (2*R*,3*R*)-dihydroxybutanedioate monohydrate, $C_{14}H_{21}ClN_3O_3^+\cdot C_4H_5O_6^-\cdot H_2O$, is the (+)-tartrate salt of (+)-norcisapride. It has been found that (+)-norcisapride has both 5-HT3 antagonistic and 5-HT4 agonistic properties and is further substantially devoid of central nervous system effects. An intramolecular N—H···O hydrogen bond forces the amido group to be roughly coplanar with the substituted benzene ring. A three-dimensional network of hydrogen bonds is formed in the crystal. The absolute configuration of (+)-norcisapride is 3*S*,4*R*.

Comment

The title compound, (I), is the (+)-tartrate salt of the (+)-enantiomer of norcisapride.



(I)

Racemic norcisapride is the principal metabolite of racemic cisapride, a widely used gastrokinetic drug (Meuldermans *et al.*, 1988). The metabolization occurs mainly *via* the cytochrome P-450 isoenzyme CYP3A4 (Bohets *et al.*, 2000). Certain therapeutic agents (*e.g.* ketoconazole) that inhibit the metabolic pathway of cisapride can give rise to undesirably high cisapride blood levels that may cause side effects.

It has been discovered that (−)-norcisapride is a potent drug for the treatment of gastro-oesophageal reflux disease, while substantially reducing adverse effects associated with the administration of racemic cisapride (McCullough & Aberg, 1998). It has also been found that (+)-norcisapride has both 5-HT3 antagonistic and 5-HT4 agonistic properties and is further substantially devoid of central nervous system effects (Heykants *et al.*, 1999).

To contribute to a better understanding of the mechanism of action of (−)- and (+)-norcisapride, the crystal structure and absolute configuration of the title compound was determined.

The absolute configuration of the (+)-norcisapride moiety is 3*S*,4*R* in view of the fact that the Flack (1983) parameter for this configuration is −0.01 (2) and that the known configuration 2*R*,3*R* for (+)-tartrate is obtained. As in the structures of

cisapride (Collin *et al.*, 1989) and cisapride tartrate (Peeters *et al.*, 1997), an intramolecular hydrogen bond between the amido N atom and the O atom of the *o*-methoxy substituent (Table 1) forces the amido moiety and the substituted benzene ring to be roughly coplanar [dihedral angle between the two least-squares planes: 10.8 (1)°]. The C-atom chain of the hydrogen tartrate ion is in an extended conformation, with the hydroxyl O atoms having a *−sc* conformation with respect to one another. The hydrogen bonds listed in Table 1 form a three-dimensional network in the crystal.

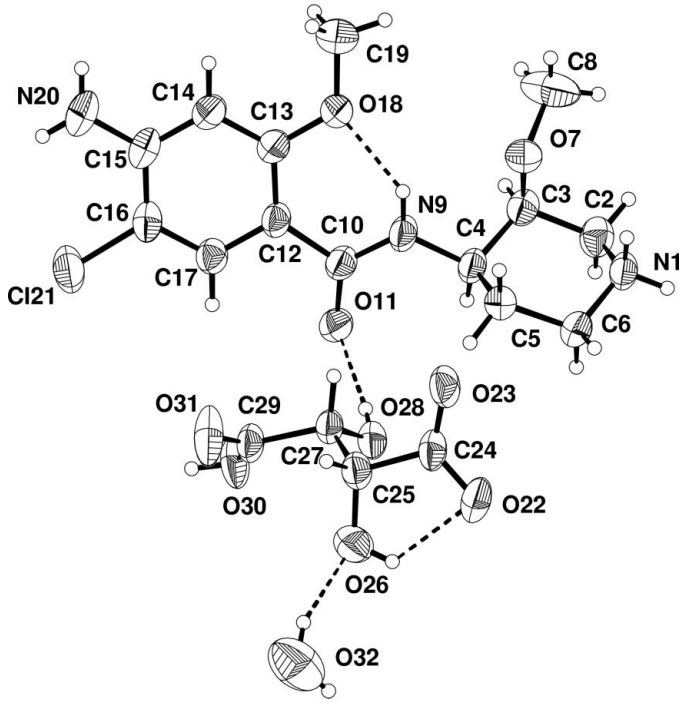


Figure 1
Perspective view of the title compound, with the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

Experimental

The title compound was obtained from the Janssen Research Foundation, Beerse, Belgium. The synthesis has been described by Heykants *et al.* (1999). Single crystals were grown by slow evaporation from a solution in methanol–water.

Crystal data

$C_{14}H_{21}ClN_3O_3^+\cdot C_4H_5O_6^-\cdot H_2O$
M_r = 481.89
Monoclinic, $P2_1$
a = 7.6086 (4) Å
b = 10.664 (1) Å
c = 14.0482 (6) Å
β = 93.980 (6)°
V = 1137.1 (1) Å^3
Z = 2
D_x = 1.407 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 39 reflections
θ = 10.8–28.0°
μ = 2.01 mm^{-1}
T = 293 K
Block, colourless
0.45 × 0.30 × 0.26 mm

Data collection

Siemens *P*4 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (*XEMP*; Siemens, 1989)
T_{min} = 0.325, T_{max} = 0.593
2935 measured reflections
2350 independent reflections
2280 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.033
θ_{max} = 69.0°
$h = -1 \rightarrow 8$
$k = -1 \rightarrow 12$
$l = -17 \rightarrow 17$
3 standard reflections
every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.107
S = 1.06
2350 reflections
295 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.069P)^2 + 0.2043P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.026 (2)
Absolute structure: Flack (1983), 220 Friedel pairs
Flack parameter = −0.01 (2)

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

D—H···A	D—H	H···A	D···A	D—H···A
N9—H9···O18	0.86	1.97	2.643 (3)	134
O26—H26···O22	0.82	2.03	2.545 (4)	120
O28—H28···O11	0.82	1.97	2.776 (3)	167
O32—H32*A*···O26	0.85	1.96	2.764 (5)	158
N1—H1*A*···O11^{i}	0.90	2.21	2.953 (3)	140
N1—H1*B*···O22^{ii}	0.90	1.86	2.728 (4)	161
N20—H20*A*···O23^{iii}	0.86	2.16	2.955 (4)	155
N20—H20*B*···O31^{iv}	0.86	2.41	2.970 (4)	123
O30—H30···O23^{v}	0.82	1.72	2.535 (3)	171
O32—H32*B*···O28^{vi}	0.85	2.34	3.107 (5)	150

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

The positions of the H atoms of the water molecule were obtained with the program *HYDROGEN* (Nardelli, 1999). Those of the OH and methyl groups were found from a circular difference Fourier synthesis. The remaining H atoms were calculated geometrically. All H atoms were included in the refinement, but constrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed at $1.25U_{eq}$ of their parent atoms.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *DIAMOND* (Bergerhoff, 1996); software used to prepare material for publication: *PARST* (Nardelli, 1983), *PLATON* (Spek, 1998) and *WinGX* (Farrugia, 1999).

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
Bergerhoff, G. (1996). *DIAMOND*. Gerhard-Domagk-Straße 1, Bonn, Germany.
Bohets, H., Lavrijsen, K., Hendrickx, J., Van Houdt, J., Van Genechten, V., Verboven, P., Meuldermans, W. & Heykants, J. (2000). *Br. J. Pharmacol.* **129**, 1655–1667.
Collin, S., Vercauteren, D. P., Evrard, G., Durant, F., Tollenaere, J. P. & Moereels, H. (1989). *J. Mol. Struct.* **214**, 159–175.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Heykants, J., Megens, A., Meuldermans, W. & Schuurkes, J. (1999). Patent No. WO9902496.
McCullough, J. & Aberg, A. (1998). Patent No. WO9640133.
Meuldermans, W., Vanpeer A., Hendrickx, J., Lauwers, W., Swysen, E., Bockx, M., Woestenborghs, R. & Heykants, J. (1988). *Drug Metab. Dispos.* **16**, 403–409.

Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.
Nardelli, M. (1999). *J. Appl. Cryst.* **32**, 563–571.
Peeters, O. M., Blaton, N. M. & De Ranter, C. J. (1997). *Acta Cryst.* C**53**, 597–599.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Siemens (1989). *XEMP*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Siemens (1996). *XSCANS*. Version 2.2. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Spek, A. L. (1998). *PLATON*. University of Utrecht, The Netherlands.