Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

2(*S*)-Amino-3-[1*H*-imidazol-4(5)-yl]-propyl cyclohexylmethyl ether dihydrochloride and 2(*S*)-amino-3-[1*H*-imidazol-4(5)-yl]propyl 4-bromobenzyl ether dihydrochloride

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Received 16 March 2000
Accepted 5 April 2000

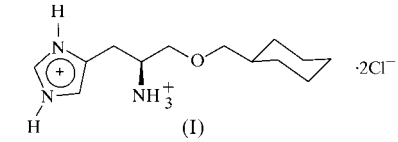
Data validation number: IUC0000099

(Cyclohexylmethyloxymethyl)(1*H*-imidazol-4-iomethyl)-(*S*)-ammonium dichloride, $C_{13}H_{25}N_3O^+\cdot 2Cl^-$, and (4-bromobenzyl)(1*H*-imidazol-4-iomethyl)-(*S*)-ammonium dichloride, $C_{13}H_{18}BrN_3O^+\cdot 2Cl^-$, are model compounds with different biological activities for evaluation of the histamine H3-receptor activation mechanism. Both title compounds occur in almost similar extended conformations.

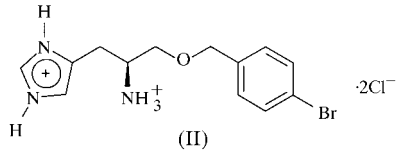
Comment

The histamine H3-receptor is located on neurones of the central and autonomic nervous system where it regulates the release of histamine and some other neurotransmitters (Arrang *et al.*, 1983; Schlicker *et al.*, 1994; Hill *et al.*, 1997). Many possible therapeutic targets for H3-receptor ligands have been suggested, such as, Alzheimer's disease, narcolepsy, schizophrenia and epilepsy (Leurs *et al.*, 1995; Stark *et al.*, 1996).

2(*S*)-Amino-3-[1*H*-imidazol-4(5)-yl]propyl cyclohexylmethyl ether dihydrochloride, (I), and 2(*S*)-amino-3-(1*H*-imidazol-4(5)-yl)propyl 4-bromobenzyl ether dihydrochloride, (II), were synthesized by Kovalainen *et al.* (1999) for evaluation of the histamine H3-receptor activation mechanism. The crystal structures of (I) and (II) were determined to reveal the absolute configuration, the low-energy conformation, and to further evaluate histamine H3-receptor–ligand interactions.



(I)



(II)

Both compounds crystallize in the orthorhombic system with one cation and two chloride ions in the asymmetric unit. The imidazole ring and amino group are protonated in the both structures. For compound (I), the non-bonded intramolecular distances N3···C14 and N3···O9 are 9.772 (4) and 5.545 (3) Å, respectively, and for compound (II), the distances N3···C14, N3···O9 and N3···Br1 are 9.015 (5), 5.406 (4) and 10.525 (3) Å, respectively.

Experimental

The title compounds were synthesized by the coupling of *N*,*N*-diprotected L-histidinol alkoxide and corresponding halides in Williamson ether syntehesis (Kovalainen *et al.*, 1999). Colorless crystals suitable for X-ray studies were obtained by diffusion method from propanol/ethyl acetate for (I) and 2-propanol/ethanol/hexane for (II)

Compound (I)

Crystal data

$C_{13}H_{25}N_3O^{2+}\cdot 2Cl^-$
$M_r = 310.26$
Orthorhombic, $P2_12_12_1$
$a = 7.8270\ (4)$ Å
$b = 12.7936\ (8)$ Å
$c = 17.3523\ (12)$ Å
$V = 1737.58\ (18)$ Å^3
$Z = 4$
$D_x = 1.186$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from all reflections
$\theta = 3.05$–$27.88°$
$\mu = 0.371$ mm^{-1}
$T = 173\ (2)$ K
Block, colourless
$0.25 \times 0.20 \times 0.10$ mm

Data collection

Nonius KappaCCD diffractometer
φ scans
Absorption correction: empirical (Blessing, 1995)
$T_{min} = 0.913$, $T_{max} = 0.964$
10 810 measured reflections
4090 independent reflections
2791 reflections with $I > 2\sigma(I)$
$R_{int} = 0.062$
$\theta_{max} = 27.88°$
$h = -9 \rightarrow 10$
$k = -12 \rightarrow 16$
$l = -22 \rightarrow 20$
no standard reflections
every no reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F) = 0.046$
$wR(F^2) = 0.084$
$S = 1.009$
4090 reflections
173 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0192P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.25$ e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = −0.11 (5)

Compound (II)

Crystal data

$C_{13}H_{18}BrN_3O^{2+}\cdot 2Cl^-$
M_r = 383.11
Orthorhombic, $P2_12_12_1$
a = 7.5530 (2) Å
b = 12.9964 (6) Å
c = 17.7800 (9) Å
V = 1745.32 (13) Å^3
Z = 4
D_x = 1.458 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from all reflections
θ = 2.93–27.88°
μ = 2.660 mm^{-1}
T = 173 (2) K
Block, colourless
0.50 × 0.10 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer
φ scans
Absorption correction: empirical (Blessing, 1995)
T_{min} = 0.3497, T_{max} = 0.7768
10 776 measured reflections
4093 independent reflections
2864 reflections with $I > 2\sigma(I)$
R_{int} = 0.053
θ_{max} = 27.88°
$h = -8 \rightarrow 9$
$k = -17 \rightarrow 14$
$l = -23 \rightarrow 17$
no standard reflections
every no reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.047
$wR(F^2)$ = 0.090
S = 1.037
4093 reflections
182 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0230P)^2 + 0.7817P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.56 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = −0.005 (10)

In the refinements, 1744 and 1724 Friedel reflections were used for (I) and (II), respectively. The H atoms were placed at calculated positions and refined as riding using *SHELXL*97 (Sheldrick, 1997) defaults; N—H = 0.86, C—H = 0.93 and C—H(methyl) = 0.96 Å.

For compounds (I) and (II), data collection: *DENZO* (Nonius, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *DENZO*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997) and *WINGX* (Farrugia, 1999); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997) and *WINGX*.

References

Arrang, J. M., Garbarg, M. & Schwartz, J. C. (1983). *Nature*, **302**, 832–837.
Blessing, R. H. (1995). *Acta Cryst.* A**51**, 33–38.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Hill, S. J., Ganellin, C. R., Timmerman, H., Schwartz, J. C., Shankley, N. P., Young, J. M., Schunack, W., Levi, R. & Haas, H. L. (1997). *Pharmacol. Rev.* **49**, 253–278.
Kovalainen, J. T., Christiaans, J. A. M., Kotisaari, S., Laitinen, J. T., Männistö, P. T., Tuomisto, L. & Gynther, J. (1999). *J. Med. Chem.* **42**, 1193–1202.
Leurs, R., Vollinga, R. C. & Timmerman, H. (1995). *Prog. Drug Res.* **45**, 107–165.
Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods Enzymol.* **276**, 307–326.
Schlicker, E., Malinowska, B., Kathmann, M. & Göthert, M. (1994). *Fundam. Clin. Pharmacol.* **8**, 128–137.
Sheldrick, G. M. (1997). *SHELXL*97 and *SHELXS*97. University of Göttingen, Germany.
Stark, H., Schlicker, E. & Schunack, W. (1996). *Drugs Future*, **21**, 507–520.