# Synthesis and crystal structure of (9*s*)-*N*-methyl-3-azabicyclo[3.3.1] nonan-9-yl (cyclopentyl)(hydroxy)(2-thienyl)acetate hydrochloride

**Yan-Qing Liu[b], He Liu[a,b]*, Bo-hua Zhong[a], Yu-Lin Deng[b] and Ke-liang Liu[a]**

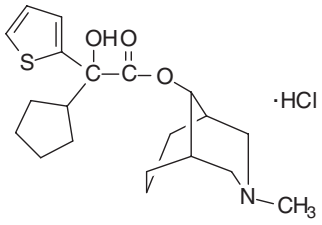
[a]*No.7 Department, Beijing Institute of Pharmacology and Toxicology, Beijing 100850. P. R. China*

[b]*School of Life Science and Technology, Beijing Institute of Technology, Beijing 100081, P. R. China*

(9*s*)-*N*-methyl-3-azabicyclo[3.3.1]nonan-9-yl (cyclopentyl)(hydroxy)(2-thienyl)acetate hydrochloride, a more effective muscarinic receptor antagonist, was synthesised and its crystal structure elucidated by X-ray crystallography.

**Keywords:** synthesis, crystal structure, muscarinic receptor antagonist

Over the past century, classical anticholinergic drugs have been widely used for the treatment of certain diseases, such as chronic obstructive pulmonary diseases, Alzheimer's disease and urinary incontinence. Most of the muscarinic receptor antagonists comprise of a chiral tertiary α-hydroxy acid as a key component.[1] We have engaged in the synthesis and biological activity study of anticholinergic drugs for many years.[2] Recently we synthesised a potent muscarinic receptor antagonist, (9*s*)-*N*-methyl-3-azabicyclo[3.3.1]nonan-9-yl (cyclopentyl)(hydroxy)(2-thienyl)acetate hydrochloride which was composed of a tertiary hydroxy acid and (9*s*)-*N*-methyl-3-azabicyclo[3.3.1]nonane structure. The biological results suggest that the title compound is more effective at treating centric and peripheral choline dysfunction.[3] The title compound was synthesised from methyl (cyclopentyl)(hydroxy)(2-thienyl)acetate and (9*s*)-*N*-methyl-3-azabicyclo[3.3.1]nonan-9-ol. Crystals of the title compound suitable for X-ray structure determination were obtained from the filtrate by slow evaporation of a methanol solution.




The X-ray ORTEP structure of the title compound with atomic labelling is shown in Fig. 1. The unit cell contains two asymmetry-independent molecules with no significant difference in their structure and two discrete $Cl^-$ anions. The overall conformation is similar in both molecules. The title compound is composed of a tertiary hydroxy acid and a bicyclo structure of 3-azabicyclo[3.3.1]nonane. The nitrogen atom of the piperidine ring is protonated. The bicyclic structure adapts a twin-chair conformation, this is the most favoured conformation for the bicyclo[3.3.1]nonane ring system.[4] In the cyclohexane ring, atoms C(3) and C(8) deviate from the C(1)–C(2)–C(4)–C(5) plane by –0.4229 and 0.6811 Å, respectively, for another molecule –0.5465 and 0.7186 Å. In the piperidine ring, atoms C(8) and N(1) deviate from the C(1)–C(5)–C(6)–C(7) plane by 0.7627 and –0.5084 Å, respectively, for another molecule –0.5030 and 0.7821 Å. Thus, both molecules show deviation from ideal chair conformation.[5]

As shown in Fig. 2, a zigzag quasi-one dimensional liner structure was formed through O–H···Cl and N–H···Cl hydrogen bonds in which the $Cl^-$ anions link the O atom of the hydroxy groups the protonated N atoms of 3-azabicyclo[3.3.1]nonane in the adjacent molecule. The O···Cl separations are 3.192 and 3.228 Å with the H···Cl separations are 2.342 and 2.462 Å, the bond angles are 179.66 and 155.82°; The N···Cl separations are 3.055 and 3.101 Å with the H···Cl separations are 2.257 and 2.271 Å, the bond angles are 146.16 and 151.36°, falling into the normal range of the O···Cl and N···Cl separation for hydrogen bonding.[6]

* Correspondent. E-mail: hliuamms@yahoo.com

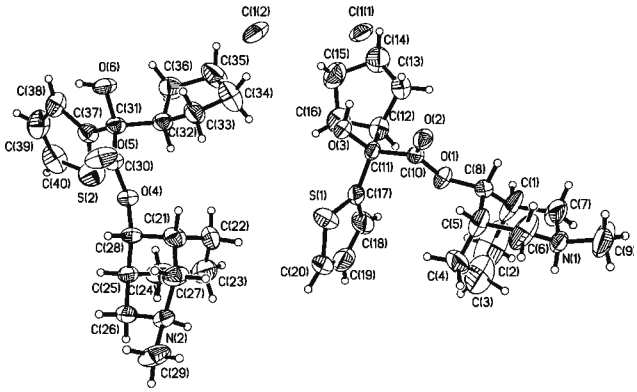



**Fig. 1** The structure of the title compound, showing 50% probability displacement ellipsoids and atom numbering scheme.

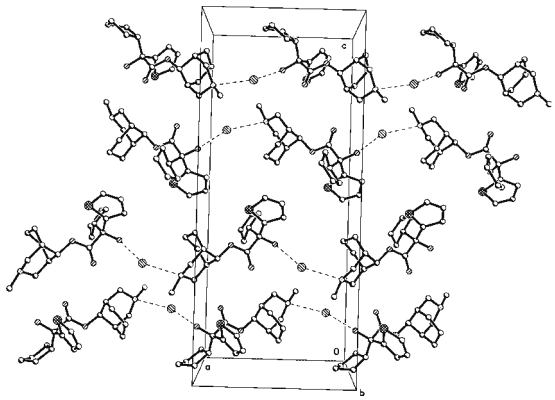


**Fig. 2** The molecular packing in the title compound, showing the quasi-one dimensional structure with hydrogen bonding.

## Experimental

All the reagents for syntheses were commercially available and used without further purification or purified by standard methods prior to use. Melting points were determined using a RY-1 apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C analyzer. $^1$H NMR spectra were measured in $CDCl_3$ using a multinuclear FT-NMR spectrometer ARX300 (Bruker). Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. Methyl (cyclopentyl) (hydroxy) (2-thienyl)acetate was synthesised by addition of Grignard reagents to dimethyl oxalate as described in the literature.[7] (9*s*)-*N*-methyl-3-azabicyclo[3.3.1]nonan-

9-ol was synthesised as a sole product by reduction of *N*-methyl-3-azabicyclo[3.3.1]nonan-9-one using $PtO_2$ as catalyst.[8]

*Synthesis of (9s)-N-methyl-3-azabicyclo[3.3.1]nonan-9-yl (cyclopentyl)(hydroxy)(2-thienyl)acetate hydrochloride*: Methyl (cyclopentyl)(hydroxy)(2-thienyl)acetate (2.6 g, 11 mmol) and (9*s*)-*N*-methyl-3-azabicyclo[3.3.1]nonan-9-ol (1.5 g, 10 mmol) were dissolved in anhydrous *n*-heptane (100 ml), NaH (0.5 g assay 80%) was added. The solution was refluxed for 3 h. The solvent was removed under reduced pressure; the residue was dissolved in ether (150 ml), washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to dryness. The product was purified by flash-chromatography (chloroform/methanol, 9:1) and the title compound was isolated as an oil (3.1g, 79%). $^1$H NMR ($CDCl_3$): δ 7.24 (m, 1H), 7.12 (m, 1H), 7.08 (m, 1H), 5.01 (s, 1H), 3.81 (m, 2H), 2.91 (m, 2H), 2.87 (s, 3H), 2.85 (m, 2H), 2.31 (s, 1H), 2.18 (s, 1H), 1.92 (m, 2H), 1.40–1.85 (m, 12H). MS (ESI): 364.2 $(M+1)^+$.

The oil was dissolved in $Et_2O$, 1 M HCl/$Et_2O$ was dropped slowly. The mixture was stirring at room temperature for 1h. The precipitation was filtered and washed with cooled $Et_2O$, dried under vacuum. (9*s*)-*N*-methyl-3-azabicyclo[3.3.1]nonan-9-yl (cyclopentyl)(hydroxy)(2-thienyl)acetate hydrochloride was obtained as a white precipitate. m.p. 189–190°C. $^1$H NMR ($CDCl_3$): δ 10.48(br, 1H), 7.24(m, 1H), 7.13(m, 1H), 6.95(m, 1H), 5.04(s, 1H), 3.86(m, 2H), 3.31(m, 2H), 2.94(s, 3H), 2.84(m, 2H), 2.29(s, 1H), 2.17(s, 1H), 1.90(m, 2H), 1.40–1.75 (m, 12H). Anal. Calcd for $C_{20}H_{30}ClNO_3S$: C, 66.06; H, 7.56; N, 3.50. Found: C, 66.11; H, 7.59; N, 3.43.

*Crystal data:* $C_{20}H_{30}ClNO_3S$, M*r* = 399.96, Orthorhombic, $P2_12_12_1$, $a$ = 11.595(3) Å, $b$ = 13.648(3) Å, $c$= 26.806(6) Å, $V$ = 4242.2(18) Å$^3$, $D_x$ = 1.252 g cm$^{-3}$, $Z$ = 8, μ = 0.297 mm$^{-1}$, $T$ = 293(2) K. A yellow crystal with dimensions of 0.20 mm × 0.18 mm × 0.14 mm was mounted on a Bruker Smart 1000 CCD diffractometer equipped with a graphite monochromator for data collection. The determination of unit cell parameters and data collections was performed with Mo Kα radiation (λ = 0.71073 Å) and unit cell dimensions were obtained with least-squares refinements. A total of 31636 reflections with 7475 independent ones with $R_{int}$ = 0.0482 and 4989 observed reflections with $I > 2\sigma(I)$ were collected in the range of 1.55 < θ < 26.472° by an ω/θ scan mode at 293(2) K. All data were corrected by using SADABS method.[9] The structure was solved by direct methods using SHELXS-97 and refined with SHELXL-97.[10] All the other non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was carried out by full matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on $F^2$. The hydrogen atoms were added theoretically, and riding on the concerned atoms and refined with fixed thermal factors. The weighting scheme was $w = 1/[\sigma^2(F_o^2) + (0.0962P)^2 + 3.3298P]$, where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to the final $R$ = 0.0747 and $wR$ = 0.1868. $S$ = 1.033. Molecular graphics were drawn with the program package XP.[11]

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications (CCDC No. 233063). Copies of available materials can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 int. code (+44)(1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

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