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Tizanidine and tizanidine hydrochloride: on the correct tautomeric form of tizanidine

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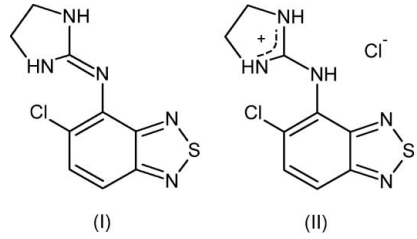
A crystallization series of tizanidine hydrochloride, used as a muscle relaxant for spasticity acting centrally as an α_2-adrenergic agonist, yielded single crystals of the free base and the hydrochloride salt. The crystal structures of tizanidine [systematic name: 5-chloro-*N*-(imidazolidin-2-ylidene)-2,1,3-benzothiadiazol-4-amine], $C_9H_8ClN_5S$, (I), and tizanidine hydrochloride {systematic name: 2-[(5-chloro-2,1,3-benzothiadiazol-4-yl)amino]imidazolidinium chloride}, $C_9H_9ClN_5S^+\cdot Cl^-$, (II), have been determined. Tizanidine crystallizes with two almost identical molecules in the asymmetric unit (r.m.s. deviation = 0.179 Å for all non-H atoms). The molecules are connected by N—H···N hydrogen bonds forming chains running along [$2\bar{1}1$]. The present structure determination corrects the structure determination of tizanidine by John *et al.* [*Acta Cryst.* (2011), E**67**, o838–o839], which shows an incorrect tautomeric form. Tizanidine does not crystallize as the usually drawn 2-amino–imidazoline tautomer, but as the 2-imino–imidazolidine tautomer. This tautomer is present in solution as well, as shown by ^{1}H NMR analysis. In tizanidine hydrochloride, cations and anions are connected by N—H···Cl hydrogen bonds to form layers parallel to (100).

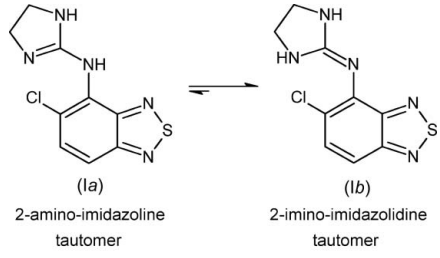
Comment

Diseases like brain or spinal cord injury (BCI and SCI), multiple sclerosis (MS), stroke and traumatic brain injuries are often associated with spasticity and involuntary muscle tension, stiffening, or contraction resulting in abnormal movement of extremities. These movements are caused by excessive motor activity resulting from injured upper motor neurons in the spinal cord no longer sending normal information from the brain to the nerve cells in the muscles. Over 12 million people are affected by spasticity worldwide (Kamen *et al.*, 2008). A huge number of active pharmaceutical ingrediants (APIs) (*e.g.* tetracepam, flupirtin, baclofen, pridinol, tolperison, eperison, or methocarbamol) have been developed for the management of spasticity over the past few decades, each with its own receptor specificity giving it a unique pharmacological effect. One of these is tizanidine and its currently applied hydrochloride salt.



Scheme 1

The free base of tizanidine, (I), was first synthesized by Neumann (1974) in the laboratories of Sandoz–Wander Inc., currently known as Novartis AG. It was patented as an antitremor and antirigor agent together with other 2,1,3-benzothiadiazole derivatives. It can exist in two possible tautomers, but only in the patent is the capability of tautomerism from 2-amino–imidazoline (I*a*) to 2-imino–imidazolidine (I*b*) mentioned (Scheme 2). In the common literature for chemistry and pharmacology (*e.g.* Falbe & Regitz, 1992; O'Neil, 2006; Mutschler *et al.*, 2008; Bruchhausen *et al.*, 1994; Aktories *et al.*, 2009) and in all related publications only the 2-amino–imidazoline tautomer is mentioned. Also the latest structure determination from single-crystal diffraction data by John *et al.* (2011) claimed that this tautomer would exist in the solid state. In this context, a recent paper (Cruz-Cabeza & Groom, 2011) reporting on wrong tautomeric assignments in published structures is relevant.



Scheme 2

To date the most common and orally administered salt form of tizanidine is its hydrochloride salt, (II), marketed by Novartis AG under the registered trade name Sirdalud™ or Zanaflex™ and approved by the US Food and Drug Administration (FDA) in November 1996 for use in adults for spasticity. Tizanidine hydrochloride has been shown to act as an α_2-adrenergic agonist (Turski *et al.*, 1986; Kameyama *et al.*, 1986). Its mechanism of action is currently under investigation and has not been fully clarified, but it is believed that the pharmacodynamic effects of tizanidine are linked to its α_2-adrenergic agonist properties; its imidazolidine receptor binding may also play a role (Bes *et al.*, 1988; Eyssette *et al.*, 1988; Muramatsu & Kigoshi, 1992; Coward, 1994; Milanov & Georgiev, 1994; Landau, 1995; Wagstaff & Bryson, 1997; Mirbagheri *et al.*, 2010; Kaddar *et al.*, 2011).

Polymorph screening on the hydrochloride salt of tizanidine was performed by crystallizing the compound from a variety of

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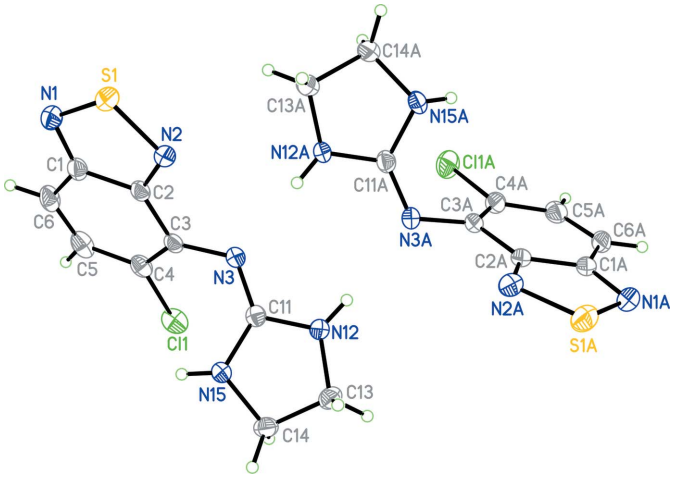

Figure 1
Perspective view of the two molecules in the asymmetric unit of tizanidine, (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as small spheres of arbitrary radii.

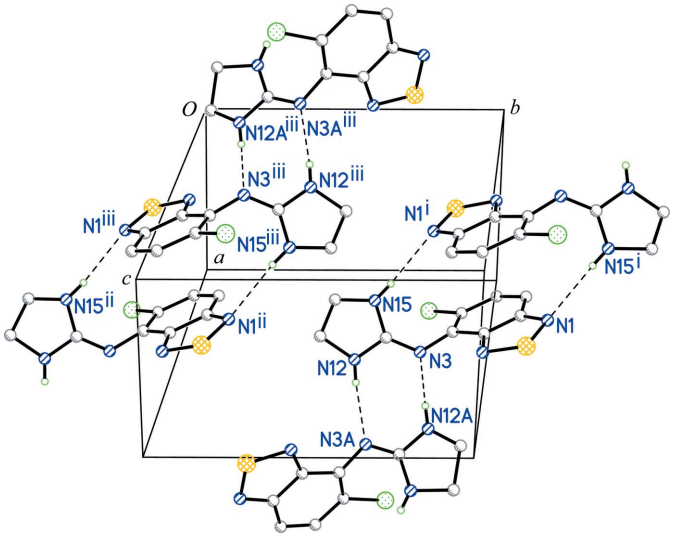

Figure 2
Packing diagram of tizanidine, (I). H atoms not involved in hydrogen bonds have been omitted for clarity and hydrogen bonds are drawn as dashed lines. [Symmetry codes: (i) $-x+1, -y+2, -z+1$; (ii) $x, y-1, z$; (iii) $-x+1, -y+1, -z+1$.]

different solvents using various methods. The crystallization experiments resulted in single crystals suitable for X-ray diffraction of the solvent-free compounds (I) and (II). New polymorphs or pseudopolymorphs were not obtained.

Although the crystal structure of the free base has already been published, a redetermination was necessary to clarify its tautomeric form in the solid state. Additionally ^{1}H NMR studies were performed to investigate the tautomeric form in solution to give additional impulse to the investigation of the mode of action of tizanidine as a muscle relaxant and the body's response to it during therapy of, for example, MS.

Tizanidine (Fig. 1) crystallizes in $P\overline{1}$ with two almost identical molecules in the asymmetric unit (r.m.s. deviation = 0.179 Å for all non-H atoms). The bond lengths in the two molecules show only insignificant differences (see Table 1). The acyclic torsion angles differ slightly in both molecules [the atoms in the second molecule of (I) are labelled with the suffix *A*] [C4—C3—N3—C11 = −55.7 (2)°, C4*A*—C3*A*—N3*A*—C11*A* = −67.4 (2)°, C3—N3—C11—N15 = −14.0 (2)° and C3*A*—N3*A*—C11*A*—N15*A* = −12.9 (3)°]. The molecules are connected by N—H···N hydrogen bonds forming chains running along [2$\overline{1}$1] (Fig. 2). The structure of tizanidine has already been published (John *et al.*, 2011). However, these authors have misplaced the H atoms at two N atoms. Instead of two protonated N atoms in the imidazolidine ring, they have placed only one H atom at one of the imidazolidine N atoms and the other one on the bridging N atom. However, their data show unequivocally that: (i) the bond from the imidazolidine C atom to the bridging N atom is a double bond [1.290 (2) and 1.296 (2) Å]; (ii) in the difference map (Fig. 3) there is no peak indicating an H atom at the bridging N atom; (iii) there are peaks in the difference map indicating that both imidazolidine N atoms are protonated. Additionally a comparison with another ten known solvent-free derivatives of (I) in the Cambridge Structural Database (CSD; Allen, 2002) revealed that all of them show the 2-imino–imidazolidine tautomeric form (I*b*) [CSD refcodes ALALEF (Saczewski *et al.*, 2011), GOLNIE (Elssfah *et al.*, 1999*a*), HIGGOU (Begum & Vasundhara, 2007), HODQOG (Elssfah *et al.*, 1999*b*), KIBRAO (Koch *et al.*, 1990), LUVPOH (Varga *et al.*, 2003), QIBBOS (Isobe *et al.*, 2000), VOVCUE01 (Schröder *et al.*, 2003), XERHOS (Kornicka *et al.*, 2006) and ZAYQOF (Dupont *et al.*, 1995)]. Finally, ^{1}H NMR measurements show that (for the –CH_2 group), instead of two different signals, as would be expected for the asymmetrical 2-amino–imidazoline tautomer (I*a*), only one signal appeared, indicating the symmetrical 2-imino–imidazolidine tautomer (I*b*). This proves that the 2-imino–imidazolidine tautomer (I*b*)

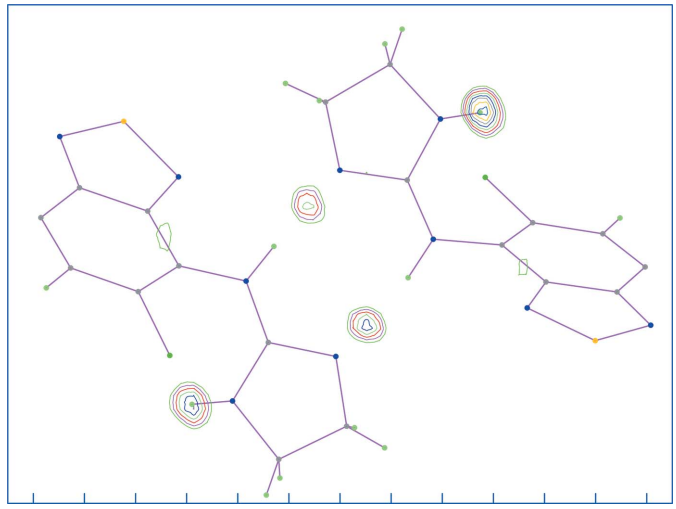

Figure 3
Difference electron-density map calculated on the basis of the data by John *et al.* (2011). H atoms bonded to N atoms have been omitted for calculating the Fourier map, but the positions of all H atoms as set by John *et al.* (2011) are shown in the figure.

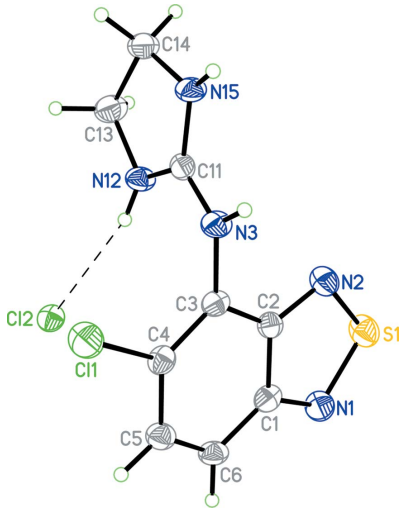

Figure 4
Perspective view of tizanidine hydrochloride, (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as small spheres of arbitrary radii.

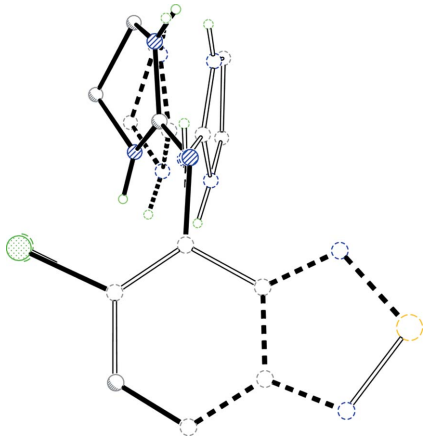

Figure 5
Least-squares fit of the two molecules of tizanidine, (I), in the asymmetric unit (full and dashed bonds distinguish between the two molecules) with the cation of tizanidine hydrochloride, (II) (open bonds). The nine atoms of the benzothiadiazole moiety have been fitted.

exists also in solution. As a result, the structure of John *et al.* (2011) has to be revised.

Tizanidine hydrochloride, (II) (Fig. 4), crystallizes with a tizanidium cation (which is protonated at the bridging N atom) and a chloride anion in the asymmetric unit. The only significant structural difference between tizanidine and the protonated molecule are the N—C bond lengths to the bridging N atom (Table 1) which are elongated in the protonated molecule. A least-squares fit of the molecular structures of the two molecules in the asymmetric unit of tizanidine and the tizanidium anion is shown in Fig. 5. The cation and neutral molecule differ in the dihedral angle between the imidazolidine and benzothiadiazole moieties [dihedral angles = 53.89 (4)/67.33 (5) *versus* 89.68 (6)°]. Whereas the mean value of the dihedral angle is approximately 60° in the neutral molecule, the ring systems are almost perpendicular in the protonated molecule. Whereas the neutral tizanidine molecules in the

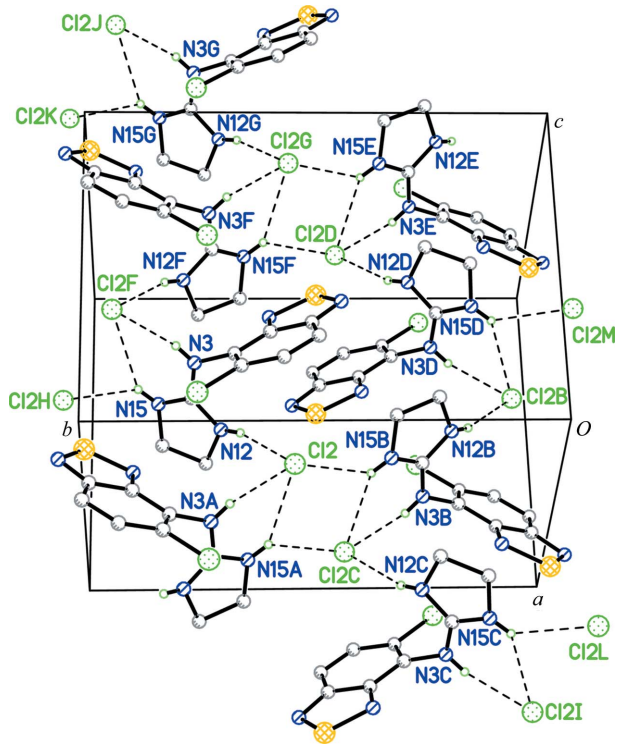

Figure 6
Packing diagram of tizanidine hydrochloride, (II). H atoms not involved in hydrogen bonds have been omitted for clarity and hydrogen bonds are drawn as dashed lines. [Symmetry codes: (A) $x, -y+\frac{3}{2}, z-\frac{1}{2}$; (B) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (C) $-x+1, -y+1, -z$; (D) $-x+1, -y+1, -z+1$; (E) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$; (F) $x, -y+\frac{3}{2}, z+\frac{1}{2}$; (G) $x, y, z+1$; (H) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (I) $-x+1, y-\frac{1}{2}, -z-\frac{1}{2}$; (J) $x, -y+\frac{3}{2}, z+\frac{3}{2}$; (K) $-x+1, y+\frac{1}{2}, -z+\frac{3}{2}$; (L) $x, -y+\frac{1}{2}, z-\frac{1}{2}$; (M) $x, -y+\frac{1}{2}, z+\frac{1}{2}$.]

crystal are only connected by N—H···N hydrogen bonds, the cations in the structure of tizanidine hydrochloride are not directly connected to each other, but *via* N—H···Cl hydrogen bonds (Fig. 6). Each chloride anion acts as an acceptor for four N—H hydrogen-bond donors, two of which are from the same cation and the remaining two from two further cations. One of the imidazolidine N—H donors forms a bifurcated hydrogen bond to two different chloride anions, whereas the other two N—H groups are bonded to only one chloride ion each. The hydrogen-bond network leads to a layer parallel to (100).

Although no further polymorph or pseudopolymorph could be obtained from the initial polymorph screening, the tautomerism of the free base of tizanidine in the solid and liquid state could be revealed. The results presented here may give further guiding principles for future examinations on derivatives of tizanidine for developments in this field of study. More to the point, it could support studies dealing with the mechanism of action of tizanidine.

Experimental

Tizanidine hydrochloride was purchased from TCI EUROPE NV Belgium (>98% purity), used as received and was found to be soluble at room temperature in methanol, ethanol, water, quinoline, morpholine, 2-picoline, *N*,*N*′-dimethylformamide, *N*,*N*′-dimethylacetamide

and dimethyl sulfoxide (DMSO). Subsequently, different methods of crystallization were employed including: (i) slurry experiments by suspending (II) in different solvents at room temperature; (ii) solvent-assisted grinding experiments by addition of several drops of solvent to the solid of (II) and grinding by hand using a mortar and pestle for several minutes at room temperature; (iii) evaporation crystallization at room temperature and at 353 K; (iv) slow or rapid antisolvent crystallization by overlaying a solution of (II) with an antisolvent (a multitude of different organic solvents, *e.g.* ketones, ethers, esters, alcohols, benzene derivatives and alkanes, were used as antisolvents for crystallization experiments); (v) recrystallization by heating to reflux with subsequent slow or fast cooling; (vi) treatment of a solution or suspension of (II) in an ultrasonic bath at room temperature; (vii) slow or rapid vapour diffusion experiments by diffusion of an antisolvent into a solution of (II) *via* the gas phase; (viii) thermal treatment using differential scanning calorimetry (DSC) performed on a DSC 131 (SETARAM) device. For the DSC, about 25–30 mg of the sample was placed in an aluminium crucible and measured from room temperature to 500 K at a rate of 3 K min^{-1} under a nitrogen atmosphere to observe phase transitions. All solids thus obtained were analysed by using X-ray powder diffraction data recorded under ambient conditions in transmission mode on a Stoe Stadi-P diffractometer with a Ge(111) monochromator and a linear position-sensitive detector using Cu $K\alpha_1$ radiation (λ = 1.5406 Å).

The ^{1}H NMR spectra for (I) and (II) were measured on a Bruker Avance 400 device at 400 MHz in tubes filled with d_6-DMSO and about 5 mg of substance. The elemental analyses (CHNS) were carried out on an Elementar (vario MICRO cube) elemental analyzer. About 1–4 mg of the samples were placed in a tin vessel and measured at 1423 K under a helium atmosphere with the addition of oxygen during the measurement.

In order to obtain single crystals of (I), the commercially available compound (II) (60 mg) was dissolved in morpholine (3 ml) in an ultrasonic bath at room temperature. Subsequently, the solution was filtered and diisopropyl ether (7 ml) was added. After 8 d, orange single crystals precipitated. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.64 (*d*, $^3J_{HH}$ = 9.2 Hz, 1H, H6), 7.52 (*d*, $^3J_{HH}$ = 9.2 Hz, 1H, H5), 6.33 (*s*, 2H, H12 and H15), 3.38 (*s*, 4H, H13*A*, H13*B*, H14*A* and H14*B*). Elemental analysis calculated for $C_9H_8ClN_5S$ (%): C 42.61, H 3.18, N 27.60, S 12.64; found (%): C 42.48, H 3.07, N 27.43, S 12.92.

For growing crystals of (II), the commercially available compound (II) (340 mg) was dissolved in water (17 ml) in an ultrasonic bath at room temperature. Subsequently, the solution was filtered and the filtrate was allowed to evaporate at room temperature. After 10 d, pale-yellow single crystals precipitated. ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.14 (*s*, 1H, H3), 8.48 (*s*, 2H, H12 and H15), 8.21 (*d*, $^3J_{HH}$ = 9.2 Hz, 1H, H6), 7.94 (*d*, $^3J_{HH}$ = 9.2 Hz, 1H, H5), 3.71 (*s*, 4H, H13*A*, H13*B*, H14*A* and H14*B*). Elemental analysis calculated for $C_9H_9Cl_2N_5S$ (%): C 37.25, H 3.13, N 24.14, S 11.05; found (%): C 37.31, H 3.23, N 23.92, S 10.88.

Compound (I)

Crystal data

$C_9H_8ClN_5S$
M_r = 253.71
Triclinic, $P\overline{1}$
a = 7.5935 (6) Å
b = 10.8712 (9) Å
c = 12.8862 (12) Å
α = 95.794 (7)°
β = 100.349 (7)°
γ = 92.125 (7)°
V = 1039.45 (15) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.55 mm^{-1}
T = 173 K
0.47 × 0.47 × 0.45 mm

Data collection

Stoe IPDS II two-circle diffractometer
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)
T_{min} = 0.784, T_{max} = 0.792
9426 measured reflections
3872 independent reflections
3537 reflections with $I > 2\sigma(I)$
R_{int} = 0.033

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.076
S = 1.06
3872 reflections
306 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Compound (II)

Crystal data

$C_9H_9ClN_5S^+\cdot Cl^-$
M_r = 290.17
Monoclinic, $P2_1/c$
a = 8.5321 (7) Å
b = 14.0679 (9) Å
c = 10.1266 (8) Å
β = 105.856 (6)°
V = 1169.24 (15) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.72 mm^{-1}
T = 173 K
0.34 × 0.31 × 0.25 mm

Data collection

Stoe IPDS II two-circle diffractometer
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)
T_{min} = 0.793, T_{max} = 0.841
9834 measured reflections
2383 independent reflections
1907 reflections with $I > 2\sigma(I)$
R_{int} = 0.076

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.080
S = 0.98
2383 reflections
167 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

All H atoms were located in Fourier difference maps. Nevertheless, H atoms bonded to C atoms were positioned geometrically and refined using a riding model with fixed individual displacement parameters [U_{iso}(H) = 1.2U_{eq}(C)], and with aromatic C—H = 0.95 Å

Table 1
Selected geometric parameters (Å, °) for tizanidine (two independent molecules) and tizanidine hydrochloride, (II).

	(I), molecule 1	(I), molecule 2 (labels have suffix *A*)	(II)
Cl1—C4	1.7434 (16)	1.7356 (17)	1.728 (2)
S1—N1	1.6196 (15)	1.6190 (15)	1.614 (2)
S1—N2	1.6181 (13)	1.6117 (15)	1.6143 (19)
N1—C1	1.347 (2)	1.346 (2)	1.351 (3)
N2—C2	1.342 (2)	1.343 (2)	1.342 (3)
N3—C3	1.3776 (19)	1.388 (2)	1.420 (2)
N3—C11	1.302 (2)	1.301 (2)	1.334 (3)
N12—C11	1.347 (2)	1.3415 (19)	1.324 (2)
N12—C13	1.461 (2)	1.440 (2)	1.460 (3)
N15—C11	1.3645 (19)	1.380 (2)	1.328 (2)
N15—C14	1.4656 (19)	1.462 (2)	1.463 (3)
C3—N3—C11	123.23 (12)	119.65 (13)	121.34 (16)

Table 2
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N12—H12···N3A	0.83 (2)	2.18 (2)	3.0006 (19)	171 (2)
N15—H15···N1^{i}	0.86 (1)	2.40 (1)	3.2078 (18)	156 (2)
N12A—H12A···N3	0.82 (2)	2.04 (2)	2.8489 (19)	172 (2)
N15A—H15A···N1A^{iv}	0.81 (2)	2.40 (2)	3.173 (2)	158.7 (18)

Symmetry codes: (i) $-x+1, -y+2, -z+1$; (iv) $-x+3, -y+1, -z+2$.

Table 3
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···Cl2^{F}	0.76 (3)	2.35 (3)	3.0843 (18)	163 (2)
N12—H12···Cl2	0.80 (3)	2.39 (3)	3.1656 (18)	164 (2)
N15—H15···Cl2^{F}	0.77 (3)	2.70 (2)	3.3131 (19)	138 (2)
N15—H15···Cl2^{H}	0.77 (3)	2.69 (3)	3.2419 (18)	131 (2)

Symmetry codes: (F) $x, -y+\frac{3}{2}, z+\frac{1}{2}$; (H) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$.

or methylene C—H = 0.99 Å. H atoms bonded to N atoms were refined freely. Only the N15—H15 distance in tizanidine was restrained, *i.e.* to 0.88 (1) Å.

For both compounds, data collection: *X-AREA* (Stoe & Cie, 2001); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *XP* (Sheldrick, 2008); software used to prepare material for publication: *SHELXL97*, *PLATON* (Spek, 2009) and *publCIF* (Westrip, 2010).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3425). Services for accessing these data are described at the back of the journal.

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