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Two enantiomerically pure cyclic arenesulfonamide hydrochloride salts

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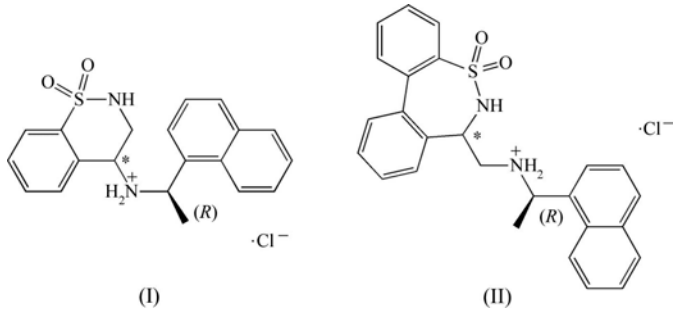
The crystal structures of *N*-[(1*R*)-1-(1-naphthyl)ethyl]-3,4-dihydro-2*H*-1,2-benzothiazin-4-aminium 1,1-dioxide chloride, $C_{20}H_{21}N_2O_2S^+\cdot Cl^-$, (I), a six-membered cyclic sulfonamide, and (1*R*)-*N*-[(5,5-dioxo-6,7-dihydrodibenzo[*d*,*f*][1,2]thiazepin-7-yl)methyl]-1-(1-naphthyl)ethanaminium chloride, $C_{26}H_{25}N_2O_2S^+\cdot Cl^-$, (II), a seven-membered cyclic sulfonamide, both representative of a novel family of agonists of the extracellular calcium sensing receptor (CaSR) of possible clinical importance, are reported. The known chirality of the naphthylethylamine precursor has enabled assignment of the absolute configuration of both compounds, which is crucial for the receptor recognition. The crystal structures, though different, reveal for these agonists a notable absence of intramolecular π–π stacking between their respective aromatic groups. This suggests a common structural feature that allows CaSR agonists to be distinguished from antagonists, since in the latter, such interactions have been shown to be important. The connectivities between molecules in the crystal structures are also different, but both involve hydrogen bonding mediated by chloride ions as a common dominant feature.

Comment

The extracellular calcium sensing receptor (CaSR) (Hofer & Brown, 2003), identified a little over a decade ago (Brown *et al.*, 1993), belongs to family 3 of the G-protein coupled receptors (GPCR). CaSR responds to extracellular calcium levels, thereby maintaining calcium homeostasis in the organism (Brown & MacLeod, 2001). Failure to maintain constant extracellular ionized calcium levels is associated with disorders such as hyperparathyroidism and osteoporosis (Brown *et al.*, 1998). Recently, several small synthetic ligands of CaSR have been developed, which act selectively at this receptor as agonists or calcimimetics. These include cinacalcet (Harrington & Fotsch, 2007), presently used clinically, and calindol, developed in our own laboratory (Kessler *et al.*, 2004).

In our continuing search for novel chemical families of CaSR ligands, two cyclic sulfonamide (sultam) compounds, (I) and (II), were recently synthesized using the aziridine-based chemistry developed by our group (Dauban & Dodd, 2000). While the (*R*)-naphthylethylamine moieties of both these compounds are common to that of calindol and cinacalcet, the sultam rings represent a major structural difference with



known CaSR ligands. Compound (I) contains a six-membered sulfonamide ring fused to a benzene ring, and (II) contains a seven-membered sulfonamide ring joining the phenyl rings of a biphenyl motif. Furthermore, the attachment of the (*R*)-naphthylethylamine moiety to the stereogenic benzylic position of the sultam platforms differs in the two compounds by the presence of an additional methylene group in (II)

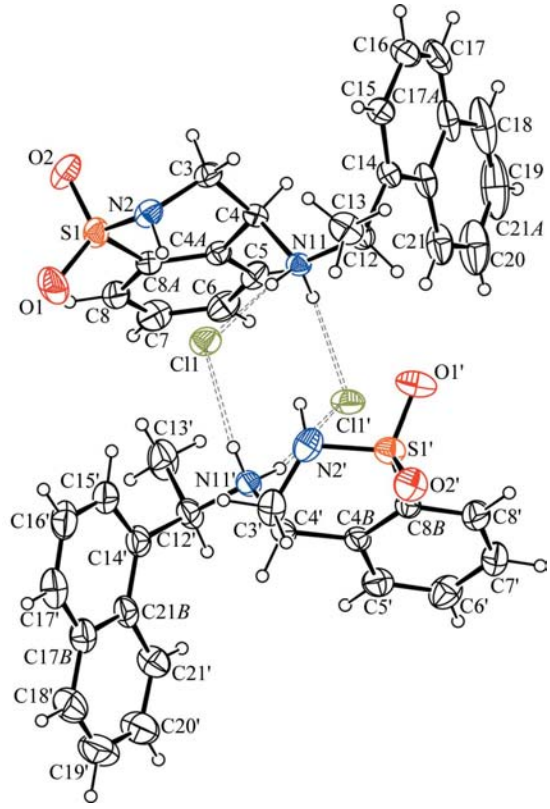


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are drawn as small spheres of arbitrary radii. The absolute configurations at atoms C4 (C4′) and C12 (C12′) are *S* and *R*, respectively, with the H atom on C4 pointing above the sulfonamide mean plane, as for the equivalent H atom of (II).

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Compounds (I) and (II) were each obtained as diastereomeric mixtures which could be separated by chromatography. In both cases, only one diastereomer of each compound was observed to be significantly active as a calcimimetic. However, attribution of the absolute configuration at the ring stereogenic centre was not possible by the usual NMR techniques. Because suitable crystals of the less active isomers of (I) and (II) could be prepared as hydrochloride salts, X-ray crystallography of these sultams was used to determine their absolute configurations. In both cases, the (*R*)-naphthylethylamine used for the synthesis of (I) and (II) allowed determination of the absolute configurations assigned here, which were confirmed by the joint anomalous dispersion effect of the Cl and S atoms present in both crystal structures. Though IUPAC nomenclature conventions attribute *S* and *R* configurations for C4 in (I) and C3 in (II), respectively, both compounds display the same spatial arrangement at the sultam stereogenic centres (Figs. 1 and 2), indicating a strong stereochemical bias by CaSR.

These two compounds crystallized in different Sohncke space groups, *viz*. $P1$ for (I) and $P2_1$ for (II), in each case having two crystallographically independent molecules, *A* and *B*, in the asymmetric unit (Figs. 1 and 2). The two molecules in the asymmetric unit differ primarily in the orientation of the naphthylethylamine fragment with respect to the sulfonamide ring. These differences are more pronounced in (I) than in (II), despite the presence of a linker shorter by one methylene unit. For (I), the overlay of the sulfonamide ring atoms highlights the deviation around the C4—N11 bond, with a change in the C14—C12—N11—C4 torsion angle from −26.9 (4) to 56.3 (4)° for C14′—C12′—N11′—C4′ (Fig. 3). For (II), the molecules almost superimpose and the N15—C16—C18—C19 torsion angle between the two ring systems is 36.1 (4)° compared with 38.7 (4)° for N15′—C16′—C18′—C19′ (Fig. 4).

The molecular dimensions in each of the two structures are essentially in agreement with expected values, in particular, those found among the few examples of six- and seven-membered sultams [only 32 and six, respectively, reported to date in the Cambridge Structural Database (Version 5.29, January 2008 update; Allen, 2002), despite the widespread biological importance of this family of compounds]. On the basis of the C—N bond distance range of 1.488 (4)–1.551 (4) Å around N11 (N11′) for (I) [N15 (N15′) for (II)], compounds (I) and (II), characterized as ammonium cations, have their positive charge localized on these N atoms rather than on the sulfonamide atom N2 (N2′). However, each Cl^- anion acts as an acceptor for several hydrogen bonds from both types of NH groups, including N2 and N2′, and the N···Cl distances [3.049 (2)–3.307 (3) Å; Tables 1 and 2] are in the expected ranges (Steiner, 1998).

The asymmetric unit of (I) consists of a μ-chloro-like dimer in which the two chloride ions link the two cations *via* N—H···Cl hydrogen bonds around a pseudo-inversion centre, forming an $R_4^2(8)$ motif (Bernstein *et al.*, 1995); the amine groups and the two chloride ions form a quasi-square plane lying almost parallel to the naphthalene group, themselves almost parallel to (121), with an N11···Cl1(Cl1′)···N11′ bridging angle of 88.5 (4)° [94.3 (4)°] and a Cl1···N11(N11′)···Cl1′ angle of 88.7 (4)° [87.8 (4)°]. The anion separation is 4.366 (5) Å.

The cations are composed of two bicyclic units articulated around an ethylamine linker, displaying an overall bent conformation at the amine group. The six-membered sultam unit fused to the benzene ring adopts a half-chair conformation, as assessed by the ring-puckering angles θ and φ (Cremer & Pople, 1975), which, for the atom sequence S1/N2/C3/C4/C4*A*/C5, are 130.5 (4) and 267.1 (5)° for (I*A*), and 128.3 (4) and 284.3 (5)° for (I*B*), with atoms N2 and C3 deviating from the S1/C8*A*/C4*A*/C4 mean plane by 0.401 (8) and 0.366 (11) Å in (I*A*), and 0.205 (10) and 0.532 (12) Å in (I*B*), respectively. The dihedral angle between the mean

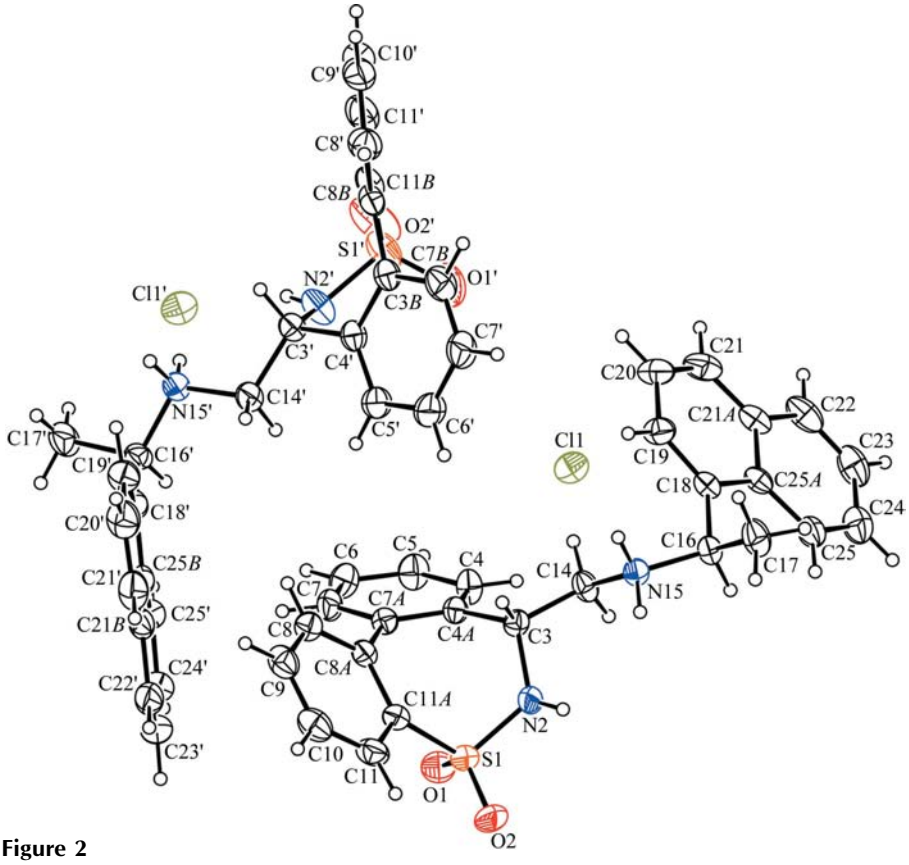

Figure 2
The molecular structure of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are drawn as small spheres of arbitrary size. The absolute configurations at atoms C3 (C3′) and C16 (C16′) are both *R*, with the H atom of C3 pointing above the sulfonamide mean plane, as for the equivalent H atom of (I).

planes of the two ring systems is 66.3 (4)° for (I*A*) and 60.9 (4)° for (I*B*), implying that the two ring systems are maintained orthogonal to each other instead of being oriented face-to-face. Weak intra- and intermolecular edge-to-face interactions and nonconventional C—H···O bonds (only C4—H4···O2$''^{i}$ is reported in Table 1) contribute to stabilizing these conformers as head-to-tail dimers, as shown in Fig. 5. The sultam rings lie on top of each other with a centre-to-centre distance above 4 Å along *b*, and the naphthalene ring systems are pushed toward the opposite parallel sides. Contiguous dimers then connect into [111] chains by intermolecular offset π–π stacking of their naphthalene ring systems. The mean planes of two adjacent naphthalene ring systems are rotated by ∼36° relative to each other, barely inclined at 8.38°, and the shortest centroid–centroid distance between two naphthyl groups is 3.869 (3) Å. The combination of these different types of interactions generates a sheet lying parallel to (10$\bar{1}$) (Fig. 5). Single C—H···O hydrogen-bonded *C*(13) and *C*(7) (Bernstein *et al.*, 1995) chains join, respectively, molecules (I*A*) and (I*B*) along the *c* and *a* axes (Table 1), thereby generating the three-dimensional framework.

In the crystal structure of (II), the molecules, which comprise a more voluminous sultam unit linked to the naphthalene ring system *via* a three-atom arm, exhibit an unfolded conformation. The linker is nearly maximally extended along the *a* direction of the crystal. The most remote benzene ring is nearly parallel to the naphthalene group, whereas the other benzene ring is tilted by *ca* 51°. The heterocyclic seven-membered ring is in a boat-shaped conformation, with an approximate mirror plane through S1 and the mid-point of the C4*A*—C7*A* bond (Fig. 2), with Cremer–Pople puckering angles of $\theta(2)$ = 1.103 (3) Å for (II*A*) [1.098 (3) Å for (II*B*)], $\theta(3)$ = 0.179 (3) Å [0.182 (3) Å], $\varphi(2)$ = 352.16 (17) Å [350.52 (19) Å] and $\varphi(3)$ = 313.1 (10)° [312.3 (11) Å].

Fig. 6 shows the contents of the unit cell, viewed down the *b*-axis direction. Unlike (I), no intermolecular π–π stacking interactions between rings are present in the crystal structure of (II). However, similar to (I), the intermolecular organization is dominated by hydrogen-bonding interactions between the chloride anions and the N atoms (Table 2). The interactions with the amine N15 (N15′) atoms form infinite $C_2^2(4)$ (Bernstein *et al.*, 1995) chains that zigzag around the helicoidal axes in the positions (0, *y*, $\frac{1}{2}$) and ($\frac{1}{2}$, *y*, 0), in a trapezoidal fashion parallel to (100). The chloride ions are separated by 4.777 (5) Å and the amine N atoms by 5.082 (5) Å. The N···Cl···N angles range between 79.4 (4) and 108.1 (4)°, whereas the Cl···N···Cl angles are between 73.2 (4) and 99.1 (4)°. The one-dimensional character of the crystal structure is evidenced by the fact that the molecules all lie parallel to (010) and form infinite *C*(7) (Bernstein *et al.*, 1995) chains *via* single C—H···O(sulfonamide) hydrogen bonds extending along [010]. Chains containing the same conformers are related to one another by the 2_1 screw axes and then held by N—H···Cl interactions. Conformers (II*A*) thereby occupy the

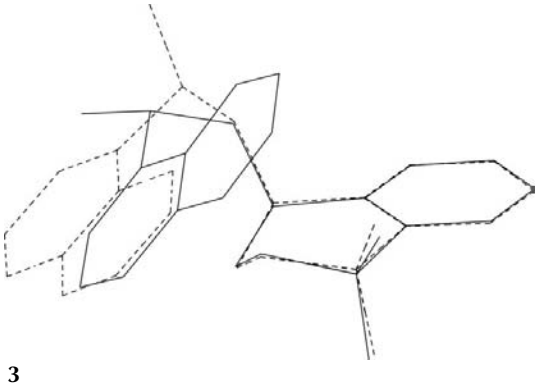

Figure 3
An overlay of atoms of the sulfonamide moieties of the two molecules of (I) in the asymmetric unit (r.m.s. deviation of 0.048 Å), showing differences in the two conformers, resulting in an overall fitting value of 1.675 Å [(I*A*) is shown with solid lines and (I*B*) with dashed lines].

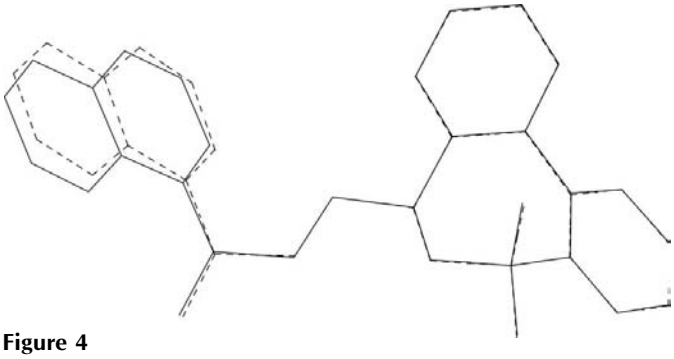

Figure 4
An overlay of atoms of the sulfonamide moieties of the two molecules of (II) in the asymmetric unit (r.m.s. deviation of 0.023 Å), showing differences in the two conformers, resulting in an overall fitting value of 0.204 Å [(II*A*) is shown with solid lines and (II*B*) with dashed lines].

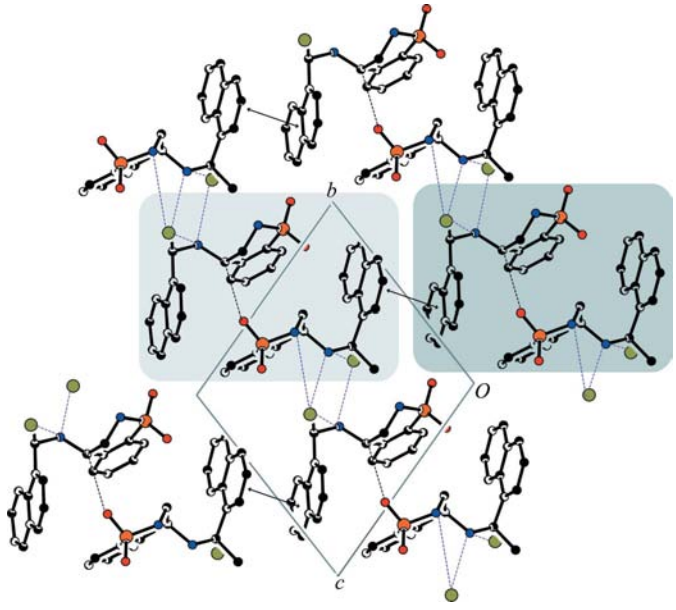

Figure 5
A view of the columnar packing of (I) in the *bc* plane. The shaded rectangles highlight the head-to-tail dimer. Dashed lines represent N—H···Cl (purple in the electronic version of the paper) and C—H···O hydrogen bonds (black), and arrows denote the intermolecular π–π stacking.

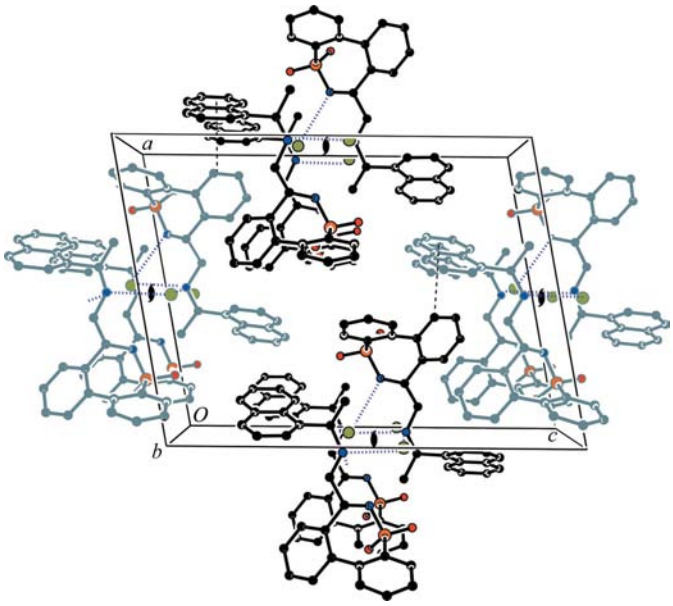

Figure 6
A view along the *b* axis of the crystal packing of (II). Molecules of conformer (II*A*) related around the twofold screw axis marked by its symbol are shown in grey and those of conformer (II*B*) are shown in black. The dashed lines represent C—H···π (arene) interactions and the dotted lines represent hydrogen bonds between N and Cl atoms.

regions at $z \simeq \frac{1}{2}, \frac{3}{2}$, *etc.*, and conformers (II*B*) the regions at $z \simeq 0, 1$, *etc*. The resulting columns dovetail with a *b*/2 spacing being adjacent columns, forming edge-to-face C—H···π (arene) contacts directed along *a*.

In conclusion, the crystal structures of the sultam derivatives (I) and (II) help to shed some light on the possible mode of interaction of these cyclic sulfonamide agonists of the calcium sensing receptor. In particular, these structures must be compared with known arene-type CaSR antagonists (or calcilytics), in which intramolecular π–π stacking has been observed and invoked as an important structural feature for their activity (Gavai *et al.*, 2005; Kessler *et al.*, 2006). In contrast, the crystal structures of both of the CaSR agonists described here revealed a notable absence of this feature between the various aromatic rings. The presence of extended conformations *versus* horseshoe-like conformations suggests a possible structural parameter that allows differentiation of these two classes of CaSR ligands.

Experimental

Compound (I) was prepared from the reaction of 1,7b-dihydroazireno[1,2-*b*][1,2]benzisothiazole 3,3-dioxide (180 mg, 1.0 mmol), obtained according to a literature procedure (Dauban & Dodd, 2000; Kiefer *et al.*, 2009), with (*R*)-naphthylethylamine (2 equivalents, 2.0 mmol, 325 µl) dissolved in tetrahydrofuran (THF). The solution was heated to 333 K and stirred for a period of 18 h with monitoring by thin-layer chromatography until completion. The resulting solution was evaporated on a rotary evaporator. The residue was purified by flash chromatography (silica gel, AcOEt/heptane 3:7) to give a mixture of two diastereoisomers in 25% yield, which were separated by high-pressure liquid chromatography (HPLC; t_{R1} = 26.8 min; t_{R2} = 31.7 min; symmetry column 4.6 × 150 mm, 1 ml min^{-1}, H_2O + 0.1%HCO_2H/CH_3CN + 0.1%HCO_2H: 80/20). The resulting compounds were transformed into their hydrochloride salts by treatment with MeOH–HCl. White needle-like crystals of the more polar diastereoisomer (corresponding to that having a retention time of 26.8 min) were obtained by slow recrystallization from methanol. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.19 (1H, *br s*), 7.94 (H, *d*, *J* = 7.3 Hz), 7.84 (1H, *d*, *J* = 7.3 Hz), 7.83 (1H, *d*, *J* = 6.5 Hz), 7.73 (1H, *d*, *J* = 7.3 Hz), 7.61–7.52 (3H, *m*), 7.50–7.44 (2H, *m*), 7.15 (1H, *d*, *J* = 6.5 Hz), 5.57 (1H, *br s*), 4.83 (1H, *q*, *J* = 6.6 Hz), 3.84 (1H, *t*, *J* = 2.3 Hz), 3.75 (1H, *d*, *J* = 15.2 Hz), 3.32 (1H, *dd*, J_1 = 15.2 Hz, J_2 = 2.3 Hz), 1.61 (3H, *d*, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 139.4, 137.7, 136.1, 134.2, 132.3, 130.5, 129.6, 129.3, 128.2, 126.4, 125.8, 125.7, 124.9, 123.3, 122.3, 53.6, 53.0, 46.2, 24.0. MS (ES+): 375.1, *M* + Na. HRMS found: 375.1166; $C_{20}H_{20}N_2NaO_2S$ requires: 375.1143. Compound (II) was prepared according to the same procedure but starting from 4b,5-dihydroazireno[1,2-*b*]dibenzo[*d*,*f*][1,2]thiazepine 7,7-dioxide (75 mg, 0.29 mmol) and (*R*)-naphthylethylamine (2 equivalents, 0.58 mmol, 95 µl) in THF at 343 K. The residue was purified by flash chromatography (silica gel, AcOEt/heptane 5:5 + 5% NEt_3) to give a mixture of two diastereoisomers in 86% yield, which were separated by HPLC (t_{R1} = 16.5 min; t_{R2} = 20.7 min; Sunfire column 2, 3 × 150 mm, 0.7 ml min^{-1}, H_2O + 0.1%HCO_2H /CH_3CN + 0.1%HCO_2H: 79/21). The resulting compounds were transformed into their hydrochloride salts by treatment with MeOH–HCl. White needle-like crystals of the more polar diastereoisomer (corresponding to that having a retention time of 16.5 min) were obtained by slow recrystallization in methanol. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21 (1H, *br s*), 8.02 (1H, *d*, *J* = 7.6 Hz), 7.92 (1H, *d*, *J* = 7.6 Hz), 7.86 (1H, *d*, *J* = 7.6 Hz), 7.74 (1H, *d*, *J* = 7.6 Hz), 7.57 (1H, *t*, *J* = 7.6 Hz), 7.54–7.48 (3H, *m*), 7.47–7.40 (3H, *m*), 7.39–7.32 (3H, *m*), 7.22 (1H, *d*, *J* = 7.6 Hz), 4.71 (1H, *q*, *J* = 6.0 Hz), 4.14 (1H, *br s*), 3.02 (1H, *br s*), 2.91 (1H, *br s*), 1.56 (3H, *d*, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 138.2 (2C), 133.9 (2C), 133.6, 133.0, 130.8 (2C), 129.9 (2C), 129.6, 129.2 (3C), 128.6, 128.5, 126.7, 125.9, 125.7, 125.6, 123.4, 122.1, 54.3, 54.2, 49.7, 21.9. MS (ES+): 429.1, *M* + H. HRMS found: 429.1667; $C_{26}H_{25}N_2NaO_2S$ requires: 429.1637.

Compound (I)

Crystal data

$C_{20}H_{21}N_2O_2S^+\cdot Cl^-$
M_r = 388.90
Triclinic, *P*1
a = 8.230 (2) Å
b = 10.927 (2) Å
c = 11.633 (3) Å
α = 103.90 (2)°
β = 106.62 (3)°
γ = 96.94 (2)°
V = 952.7 (4) Å^3
Z = 2
Mo *K*α radiation
μ = 0.33 mm^{-1}
T = 293 (2) K
0.15 × 0.10 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.88, T_{max} = 0.98
7330 measured reflections
5771 independent reflections
4862 reflections with $I > 2\sigma(I)$
R_{int} = 0.025

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.095
S = 1.02
5771 reflections
472 parameters
3 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Absolute structure: Flack (1983), 2356 Friedel pairs
Flack parameter: 0.05 (5)

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···Cl1	0.96	2.22	3.172 (3)	173
N11—H11B···Cl1	0.90	2.30	3.195 (3)	176
N11—H11A···Cl1′	0.90	2.22	3.049 (2)	153
N2′—H2′···Cl1	0.95	2.39	3.154 (3)	138
N11′—H11D···Cl1′	0.90	2.20	3.067 (3)	163
N11′—H11C···Cl1	0.90	2.34	3.229 (3)	170
C4—H4···O2′^{i}	0.98	2.36	3.114 (4)	133
C19—H19···O1^{ii}	0.93	2.60	3.465 (7)	155
C6′—H6′···O1′^{iii}	0.93	2.47	3.234 (5)	139

Symmetry codes: (i) $x, y-1, z$; (ii) $x, y, z+1$; (iii) $x-1, y, z$.

Compound (II)

Crystal data

$C_{26}H_{25}N_2O_2S^+\cdot Cl^-$
M_r = 464.99
Monoclinic, $P2_1$
a = 15.295 (4) Å
b = 7.764 (3) Å
c = 20.264 (6) Å
β = 100.48 (2)°
V = 2366.2 (13) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.28 mm^{-1}
T = 293 (2) K
0.50 × 0.22 × 0.13 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.89, T_{max} = 0.97
14090 measured reflections
8155 independent reflections
5732 reflections with $I > 2\sigma(I)$
R_{int} = 0.035

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.118
S = 1.01
8155 reflections
579 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Absolute structure: Flack (1983), 3619 Friedel pairs
Flack parameter: −0.11 (6)

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

*Cg*13 and *Cg*4 are the centroids of the C21*B*–C25*B* and C21*A*–C25*A* rings, respectively.

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···Cl1^{i}	0.98	2.34	3.307 (3)	167
N15—H15B···Cl1	0.90	2.29	3.179 (3)	168
N15—H15A···Cl1^{i}	0.90	2.20	3.098 (3)	174
N2′—H2′···Cl1′	0.81	2.54	3.299 (3)	157
N15′—H15C···Cl1′	0.90	2.18	3.072 (3)	173
N15′—H15D···Cl1′^{ii}	0.90	2.31	3.185 (3)	164
C7—H7···*Cg*13	0.93	2.80	3.569 (4)	140
C7′—H7′···*Cg*4^{iii}	0.93	2.96	3.684 (5)	136
C9′—H9′···O1′^{iii}	0.93	2.48	3.064 (6)	121

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

All H atoms were located in difference maps and then treated as riding atoms, with C—H distances of 0.93 (aromatic), 0.96 (methyl), 0.97 (methylene) or 0.98 Å (methine) and N—H distances of 0.90 Å (amine), and with U_{iso}(H) = kU_{eq}(carrier), where k = 1.5 for the methyl groups and k = 1.2 for all other H atoms. Exception was made for the sulfonamide H atoms, which were refined freely at the early stage of the refinement to highlight the sp^3 character of the sulfonamide N atom, then constrained to ride. Three floating origin restraints were generated automatically by *SHELXL97* (Sheldrick, 2008). Friedel opposites were kept unmerged, and the anomalous scattering contribution, albeit weak, of the chloride anions and S atoms [2356 Bijvoet pairs for (I) and 3619 for (II)] was exploited to confirm use of the values of the Flack (1983) parameter. The absolute configuration of each compound was assigned by reference to the unchanging (*R*)-naphthylethylamine chiral centre from the commercial source.

For both compounds, data collection: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT* (Nonius, 1999); cell refinement: *DENZO* and *COLLECT*; data reduction: *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008) and *CRYSTALBUILDER* (Welter, 2006); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *publCIF* (Westrip, 2009).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3257). Services for accessing these data are described at the back of the journal.

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