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Three tetrahydro-1,4-epoxy-1-benzazepines carrying pendent heterocyclic substituents: supramolecular structures in zero, one or two dimensions

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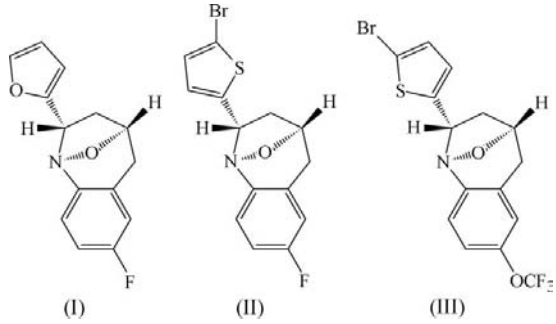
(2*SR*,4*RS*)-7-Fluoro-2-*exo*-(2-furyl)-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{14}H_{12}FNO_2$, (I), crystallizes with $Z' = 2$ in the space group $P2_1/c$. A combination of three C—H···O hydrogen bonds and one C—H···N hydrogen bond links the molecules into a complex chain of rings, and pairs of such chains are linked into a tube-like structure by two C—H···π(arene) hydrogen bonds. There are no hydrogen bonds in the structure of racemic (2*SR*,4*RS*)-2-*exo*-(5-bromo-2-thienyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{14}H_{11}BrFNOS$, (II), while the molecules of (2*S*,4*R*)-2-*exo*-(5-bromo-2-thienyl)-7-trifluoromethoxy-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{15}H_{14}BrF_3NO_2S$, (III), are linked into sheets by a combination of two C—H···O hydrogen bonds and one C—H···π(arene) hydrogen bond. The significance of this study lies in its observation of the wide variation in the patterns of supramolecular aggregation, consequent upon modest changes in the peripheral substituents.

Comment

In a continuation of our structural study of 2-substituted tetrahydro-1,4-epoxy-1-benzazepines (Acosta *et al.*, 2008; Gómez *et al.*, 2008), itself part of a programme to identify structurally novel antiparasitic compounds with new modes of action to combat both *Trypanosoma cruzi* and *Leishmania chagasi* parasites (Gómez *et al.*, 2006; Yépez *et al.*, 2006), we now report the structures of three examples, (I)–(III), carrying heterocyclic substituents at position C2 (Figs. 1–3). The synthesis of compounds (I)–(III) involved treating an appropriately substituted 2-allyl-*N*-(2-furylmethyl)aniline or 2-allyl-*N*-(2-thienylmethyl)aniline with an excess of hydrogen peroxide solution in the presence of catalytic amounts of sodium tungstate.



Under the synthetic and crystallization conditions employed, (I) and (II) both crystallize as racemic mixtures in the space group $P2_1/c$, and (I) crystallizes with $Z' = 2$. Compound (III) crystallizes as a single enantiomorph in the space group $P2_1$ and the configuration at C4 is *R*, as shown by the Flack *x* parameter (Flack, 1983). Hence, the reference molecules for the racemic compounds were selected to have the *R* configuration at C4. On this basis, the reference molecules in (I)–(III) all have the *S* configuration at C2.

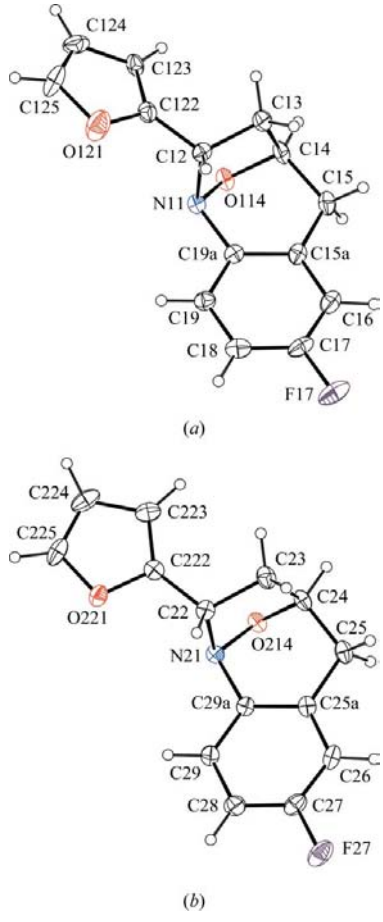


Figure 1
The structures of the two independent molecules of compound (I), *viz.* (*a*) molecule 1 and (*b*) molecule 2, showing the atom-labelling schemes. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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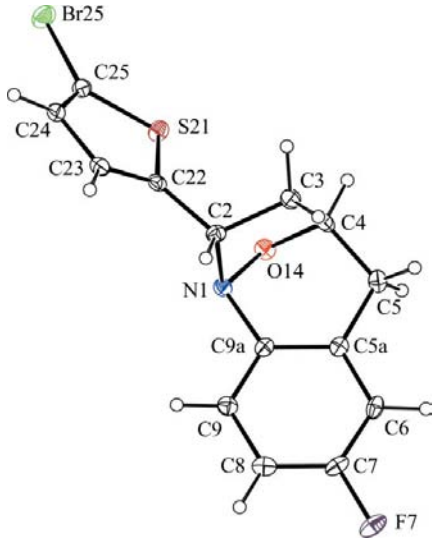

Figure 2
The molecular structure of compound (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

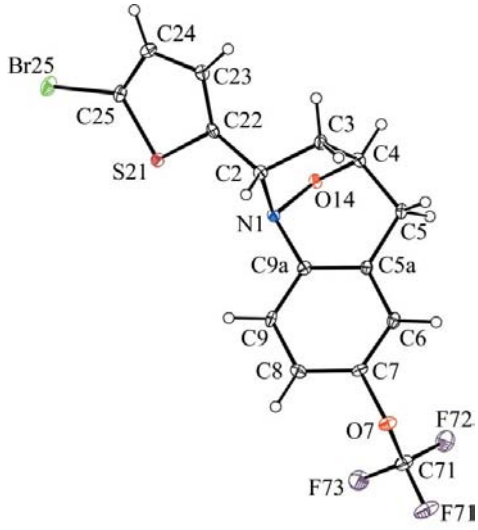

Figure 3
The molecular structure of compound (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

The shapes of the heterobicyclic ring systems in (I)–(III), as defined by the ring-puckering parameters (Cremer & Pople, 1975), are all very similar (Table 1). The five-membered rings in (II) and (III) adopt half-chair conformations, for which the ideal puckering angle φ is $(36k + 18)^\circ$, where k represents an integer, while for both independent molecules in (I) the conformations are intermediate between an envelope form (where the ideal value of φ is $36k^\circ$) and the half-chair form observed in the other examples. The conformations of the six-membered heterocyclic rings are intermediate between a half-chair form [where the idealized values of the ring-puckering angles are $\theta = 50.8^\circ$ and $\varphi = (60k + 30)^\circ$] and an envelope form (where the idealized values are $\theta = 54.7^\circ$ and $\varphi = 60k^\circ$).

The values of the N1—C2—C21—C22 torsion angle in (I)–(III), which defines the orientation of the pendent heterocyclic substituent, have rather similar values in the two independent molecules in (I) [86.7 (3) and 74.5 (3)°], but very different values in (II) [−60.1 (3)°] and (III) [36.6 (4)°], indicative of almost orthogonal orientations for the thienyl groups in these two compounds. There is no obvious simple interpretation of this observation.

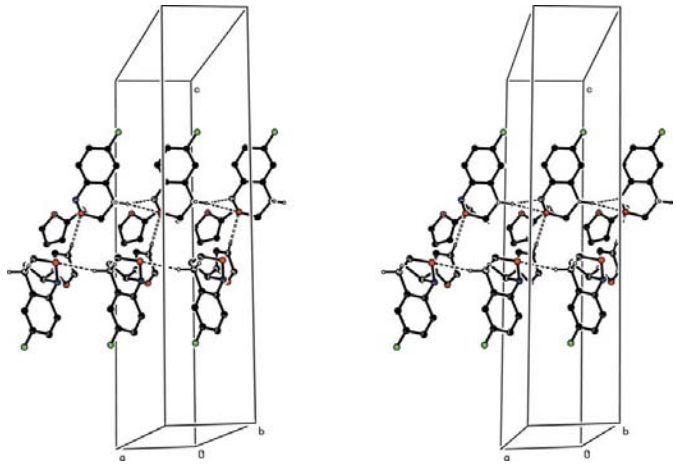

Figure 4
A stereoview of part of the crystal structure of compound (I), showing the formation of a hydrogen-bonded chain of edge-fused $R_4^3(20)$ rings along [100]. For the sake of clarity, H atoms bonded to C atoms which are not involved in the motif shown have been omitted.

Compound (I) crystallizes with $Z' = 2$ in the space group $P2_1/c$. There are six independent hydrogen bonds in the crystal structure (Table 2), leading to the formation of a structure of some complexity but which can in fact be readily analysed in terms of simple motifs. Type 1 molecules (containing atom N11), which are related by translation, are linked by a three-centre C—H···(O,N) interaction. The C—H···O and C—H···N components individually generate $C(4)$ and $C(5)$ (Bernstein *et al.*, 1995) chains, while their combination generates a $C(4)C(5)[R_1^2(3)]$ chain of rings running parallel to the [100] direction (Fig. 4). By contrast, the type 2 molecules (containing atom N21), related by translation, are linked only by a C—H···O hydrogen bond, forming a simple $C(4)$ chain parallel to [100]. The two independent molecules are linked within the asymmetric unit by a further C—H···O hydrogen bond, so that the combination of all the C—H···O and C—H···N interactions generates a chain of rings based on an $R_4^3(20)$ motif (Fig. 4). An antiparallel pair of such chains, related to one another by inversion, are then linked by two independent C—H···π(arene) hydrogen bonds to form a complex tubular structure (Fig. 5).

There are no hydrogen bonds of any type in the structure of (II). Instead, the molecules are weakly linked in pairs by a single aromatic π–π stacking interaction to form dimeric units (Fig. 6). The fluoro-substituted aryl rings of the molecules at (x, y, z) and $(1 - x, 1 - y, 1 - z)$ are parallel, with an interplanar spacing of 3.450 (2) Å; the corresponding ring-centroid separation is 3.853 (2) Å, giving a ring offset of 1.716 (2) Å.

In the structure of the trifluoromethoxy analogue, (III), by contrast, there are three hydrogen bonds, two of C—H···O

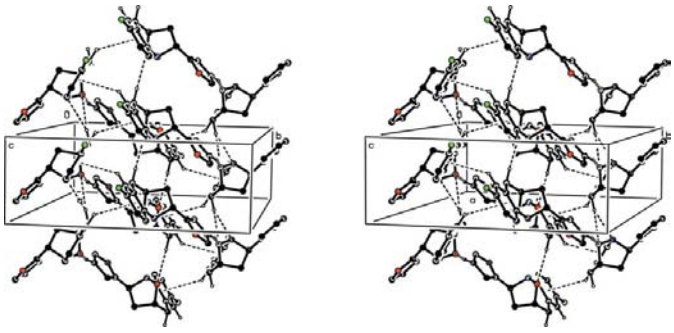

Figure 5
A stereoview of part of the crystal structure of compound (I), showing the formation of a hydrogen-bonded tube along [100], formed by the linking of an antiparallel pair of chains of rings by means of C—H···π(arene) hydrogen bonds. For the sake of clarity, H atoms bonded to C atoms which are not involved in the motif shown have been omitted.

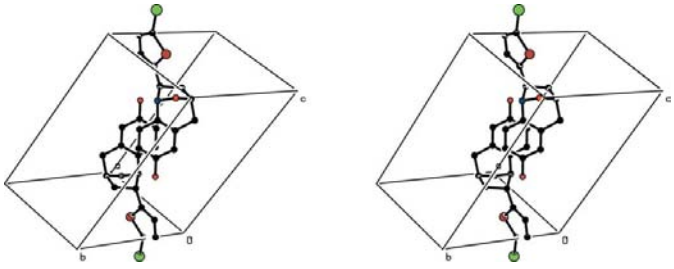

Figure 6
A stereoview of part of the crystal structure of compound (II), showing the formation of a π-stacked dimer. For the sake of clarity, all H atoms have been omitted.

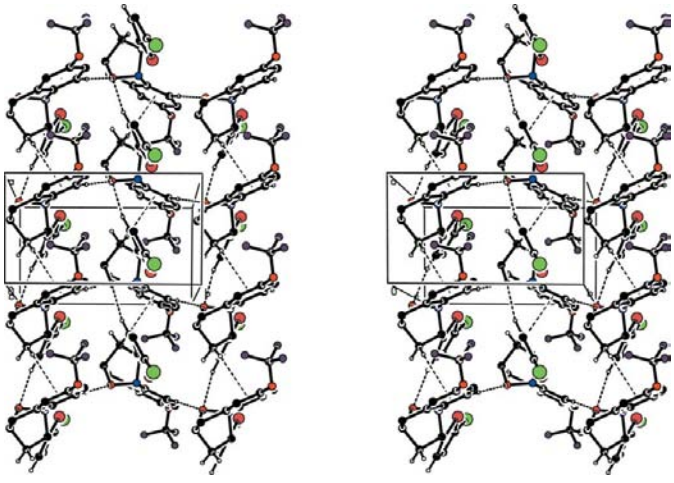

Figure 7
A stereoview of part of the crystal structure of compound (III), showing the formation of a hydrogen-bonded sheet parallel to (001). For the sake of clarity, H atoms bonded to C atoms which are not involved in the motif shown have been omitted.

type and one of C—H···π(arene) type (Table 2), and these give rise to a sheet, the formation of which is very simply analysed in terms of two simple substructures. Aryl atom C9 in the molecule at (x, y, z) acts as hydrogen-bond donor to atom O14 in the molecule at ($-x$, $\frac{1}{2}+y$, $1-z$), so linking molecules related by the 2_1 screw axis along (0, y, $\frac{1}{2}$) into a $C(5)$ chain running parallel to the [010] direction. At the same time, thienyl atom C23 at (x, y, z) acts as hydrogen-bond donor to atom O14 in the molecule at ($1+x$, y, z), thus generating by translation a $C(6)$ chain running parallel to the [100] direction. The combination of these two chain motifs then generates a sheet parallel to (001) and built from $R_4^3(20)$ rings (Fig. 7). In addition, the substructure along [100] is reinforced by the C—H···π(arene) hydrogen bond, but there are no direction-specific interactions between adjacent sheets.

Experimental

For the preparation of compounds (I)–(III), sodium tungstate dihydrate, $Na_2WO_4{\cdot}2H_2O$ (5 mol%), followed by 30% aqueous hydrogen peroxide solution (0.30 mol), were added to a stirred solution of the appropriately substituted 2-allylaniline (0.10 mol) in methanol (40 ml). The resulting mixtures were stirred at ambient temperature for periods ranging from 18 to 60 h. Each mixture was then filtered and the solvent removed under reduced pressure. Toluene (50 ml) was added to the solid residue and the resulting solution was heated under reflux for periods ranging from 6 to 8 h. After cooling each solution to ambient temperature, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica using heptane–ethyl acetate (compositions ranged from 10:1 to 60:1 *v*/*v*) as eluent. Crystallization from heptane gave crystals of compounds (I)–(III) suitable for single-crystal X-ray diffraction. For (I): yellow crystals, yield 35%, m.p. 357–358 K; MS (70 eV) *m*/*z* (%): 245 (M^+, 32), 228 (9), 215 (10), 148 (8), 123 (52), 122 (100), 94 (32). Analysis found: C 68.8, H 4.8, N 5.6%; $C_{14}H_{12}FNO_2$ requires: C 68.6, H 4.9, N 5.7%. For (II): yellow crystals, yield 61%, m.p. 380–381 K; MS (70 eV) *m*/*z* (%): 339 (M^+, ^{79}Br, 13), 309 (3), 188 (27), 148 (9), 123 (76), 122 (100). Analysis found: C 49.2, H 3.5, N 4.2%; $C_{14}H_{11}BrFNOS$ requires: C 49.4, H 3.3, N 4.1%. For (III): yellow crystals, yield 61%, m.p. 372–373 K; MS (70 eV) *m*/*z* (%): 405 (M^+, ^{79}Br, 19), 388 (13), 375 (7), 214 (6), 189 (60), 188 (100). Analysis found: C 44.3, H 2.6, N 3.5%. $C_{15}H_{11}BrF_3NO_2S$ requires: C 44.4, H 2.7, N 3.5%.

Compound (I)

Crystal data

$C_{14}H_{12}FNO_2$
M_r = 245.25
Monoclinic, $P2_1/c$
a = 5.5314 (10) Å
b = 15.430 (4) Å
c = 26.229 (6) Å
β = 92.960 (17)°
V = 2235.6 (9) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.11 mm^{-1}
T = 120 (2) K
0.38 × 0.16 × 0.09 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.969, T_{max} = 0.990
35661 measured reflections
5130 independent reflections
2690 reflections with $I > 2\sigma(I)$
R_{int} = 0.081

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.064
$wR(F^2)$ = 0.167
S = 1.03
5130 reflections
325 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.34 e Å^{-3}

Compound (II)

Crystal data

$C_{14}H_{11}BrFNOS$
M_r = 340.21
Monoclinic, $P2_1/c$
a = 8.1835 (6) Å
b = 10.9447 (8) Å
c = 14.6940 (12) Å
β = 104.969 (6)°
V = 1271.42 (17) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 3.40 mm^{-1}
T = 120 (2) K
0.45 × 0.21 × 0.08 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.307, T_{max} = 0.762
19445 measured reflections
2903 independent reflections
2026 reflections with $I > 2\sigma(I)$
R_{int} = 0.072

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.089
S = 1.05
2903 reflections
172 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.55 e Å^{-3}
$\Delta\rho_{min}$ = −0.64 e Å^{-3}

Compound (III)

Crystal data

$C_{15}H_{11}BrF_3NO_2S$
M_r = 406.22
Monoclinic, $P2_1$
a = 5.6913 (6) Å
b = 10.1187 (6) Å
c = 13.2996 (13) Å
β = 100.497 (8)°
V = 753.09 (12) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 2.91 mm^{-1}
T = 120 (2) K
0.27 × 0.22 × 0.21 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.477, T_{max} = 0.543
12890 measured reflections
3393 independent reflections
2756 reflections with $I > 2\sigma(I)$
R_{int} = 0.047

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.071
S = 1.09
3393 reflections
209 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.37 e Å^{-3}
$\Delta\rho_{min}$ = −0.36 e Å^{-3}
Absolute structure: Flack (1983), with 1567 Friedel pairs
Flack parameter: 0.094 (9)

Unique assignments of space groups were made from the systematic absences for compounds (I) and (II), both $P2_1/c$. For compound (III), the systematic absences permitted $P2_1$ or $P2_1/m$ as possible space groups; $P2_1$ was selected and confirmed by the subsequent structure analysis. All H atoms were located in difference maps and then treated as riding atoms in geometrically idealized positions, with C—H = 0.95 (aromatic, heteroaromatic and alkene), 0.99 (CH_2) or 1.00 Å (aliphatic CH) and with U_{iso}(H) = 1.2U_{eq}(C). For compound (III), the correct enantiomorph, having the *R* configuration at C4, was established by means of the Flack *x* parameter (Flack, 1983). The reference molecules in (I) and (II) were therefore chosen as those having the *R* configuration at C4.

For all compounds, data collection: *COLLECT* (Nonius, 1999); cell refinement: *DIRAX*/*LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *OSCAIL* (McArdle, 2003) and *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PRPKAPPA* (Ferguson, 1999).

Table 1
Ring-puckering parameters (Å, °) for compounds (I)–(III).

Puckering parameters for five-membered rings are defined for the atom sequence O14—N1—C2—C3—C4, apart from compound (I), where $Z' = 2$ and the atom sequences are O*x*14—N*x*1—C*x*2—C*x*3—C*x*4 for x = 1 or 2. Puckering parameters for six-membered rings are defined for the atom sequence O14—N1—C9a—C5a—C5—C4, apart from compound (I), where the atom sequences are O*x*14—N*x*1—C*x*9a—C*x*5a—C*x*5—C*x*4 for x = 1 or 2.

Compound	Five-membered ring		Six-membered ring		
	Q_2	φ_2	Q	θ	φ
(I), molecule 1	0.429 (3)	190.2 (4)	0.599 (3)	49.3 (3)	347.2 (4)
(I), molecule 2	0.432 (3)	189.4 (4)	0.599 (3)	49.2 (3)	347.0 (4)
(II)	0.455 (3)	199.7 (4)	0.626 (3)	53.2 (3)	343.2 (4)
(III)	0.447 (3)	197.2 (5)	0.623 (3)	54.1 (3)	347.0 (4)

Table 2
Hydrogen-bond parameters (Å, °) for compounds (I) and (III).

*Cg*1, *Cg*2 and *Cg*3 represent the centroids of the rings C25–C30 (C25a/C26–C29/C29a), C15a/C16–C19/C19a and C5a/C6–C9/C9a, respectively.

Compound	D—H···A	D—H	H···A	D···A	D—H···A
(I)	C15—H15*B*···O114^{i}	0.99	2.48	3.460 (3)	171
	C15—H15*B*···N11^{i}	0.99	2.61	3.538 (4)	156
	C25—H25*B*···O214^{ii}	0.99	2.57	3.539 (3)	168
	C224—H224···O114	0.95	2.39	3.271 (4)	154
	C16—H16···*Cg*1^{iii}	0.95	2.90	3.661 (3)	138
	C26—H26···*Cg*2^{iv}	0.95	2.97	3.696 (3)	134
(III)	C9—H9···O14^{v}	0.95	2.48	3.427 (5)	178
	C23—H23···O14^{ii}	0.95	2.56	3.492 (4)	167
	C3—H3*B*···*Cg*3^{ii}	0.99	2.82	3.585 (4)	134

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

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG3181). Services for accessing these data are described at the back of the journal.

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