2020

(1S)-1-Phenylethanaminium 4-{[(1S,2S)-1-hydroxy-2,3-dihydro-1H,1'H-[2,2'-biinden]-2-yl]methyl}benzoate

Christopher S. Frampton
Pharmorphix Solid State Services, A Sigma-Aldrich Company, Cambridge, UK.

Tao Zhang
Technological University Dublin, tao.zhang@tudublin.ie

Gaia A. Scalabrino
Trino Therapeutics Ltd, Ireland

See next page for additional authors

Follow this and additional works at: https://arrow.tudublin.ie/schfsehart

Recommended Citation
Frampton, C.S., Zhang, T., Scalabrino, G.A., Frankish, N. and Sheridan, H. (2012). (1S)-1-Phenylethanaminium 4-{[(1S,2S)-1-hydroxy-2,3-dihydro-1H,1'H-[2,2'-biinden]-2-yl]methyl}benzoate. Acta Crystallographica Section C, 68, 0323- 0326. doi:10.1107/S0108270112031265

This Article is brought to you for free and open access by the School of Food Science and Environmental Health at ARROW@TU Dublin. It has been accepted for inclusion in Articles by an authorized administrator of ARROW@TU Dublin. For more information, please contact arrow.admin@tudublin.ie, aisling.coyne@tudublin.ie, gerard.connolly@tudublin.ie, vera.kilshaw@tudublin.ie.
Authors
Christopher S. Frampton, Tao Zhang, Gaia A. Scalabrino, Neil Frankish, and Helen Sheridan

This article is available at ARROW@TU Dublin: https://arrow.tudublin.ie/schfsehart/352
The molecular salt, \( \text{C}_8\text{H}_{12}\text{N}^+ \cdot \text{C}_{26}\text{H}_{21}\text{O}_3^- \), contains a dimeric indane pharmacophore that demonstrates potent anti-inflammatory activity. The indane group of the anion exhibits some disorder about the \( \text{C}_1\text{C}_\text{II} \) atom, which appears common to many structures containing this group. A model to account for the slight disorder was attempted, but this was deemed unsuccessful because applying bond-length constraints to all the bonds about the \( \alpha\text{-C} \) atom led to instability in the refinement. The absolute configuration was determined crystallographically as \( \text{S,S,S} \) by anomalous dispersion methods with reference to both the Flack parameter and Bayesian statistics on Bijvoet differences. The configuration was also determined by an \textit{a priori} knowledge of the absolute configuration of the \((1\text{S})\)-1-phenylethanaminium counter-ion.

The molecules pack in the crystal structure to form an infinite two-dimensional hydrogen-bond network in the (100) plane of the unit cell.

**Comment**

The indane pharmacophore occurs in many different bioactive molecules, including the nonsteroidal anti-inflammatory indane sulindac (Clinoril, Merck) (Scheper \textit{et al.}, 2007; Shift \textit{et al.}, 1995) and the protease inhibitor indinavir (Crixivan, Merck), used as a component of highly active antiretroviral therapy (HAART) (Vacca \textit{et al.}, 1994; Lin, 1999). As part of our drug-discovery programme, we have identified a number of indanes that demonstrate smooth-muscle relaxation and inhibit mediator release (Sheridan \textit{et al.}, 1990, 1999\textit{a,b}). More recently, we have synthesized and characterized a series of dimeric indanes that demonstrate potent anti-inflammatory activity (Frankish \textit{et al.}, 2004; Sheridan, Walsh, Cogan \textit{et al.}, 2009; Sheridan, Walsh, Jordan \textit{et al.}, 2009). The title compound, (I), a single enantiomer, is the 1-phenylethanaminium salt of 4-\{[(1\text{S},2\text{S})]-1-hydroxy-2,3-dihydro-1\text{H},1'\text{H}-[2,2'\text{-biinden}]-2-yl\text{methyl}\}benzoic acid (PH46) and represents a first-in-class anti-inflammatory indane scaffold with potential therapeutic use in the treatment of inflammatory bowel disease (Frankish & Sheridan, 2012). The crystal structure and absolute stereochemistry determination of (I) are described here.

The structure of (I) is shown in Fig. 1. The inden-2-yl group, defined by atoms C18–C26, demonstrates disorder in the position of the C—C and C=C bonds in the five-membered ring. The disorder manifests itself in the appearance of three...
potential H-atom positions in a difference Fourier synthesis about each of atoms C19 and C26, both α to atom C18. The potential disorder in this group was also revealed through a Hirshfeld rigid-bond test (Hirshfeld, 1976), where the differences in the components of the anisotropic displacement parameters along the C18—C19 and C18—C26 bonds exceed 6 s.u.

A simple Conquest (Macrae et al., 2008) search of the Cambridge Structural Database (CSD, Version 5.33; Allen, 2002) for inden-2-yl fragments as shown in (II) (see Scheme), where R1 is defined as any substituent other than hydrogen, returned a total of 33 entries. The disorder present in the inden-2-yl fragment was documented in a number of structures and the use of a two-part disorder model to separate the two components was attempted [see, for example, CSD refcodes APOVUX (Nikitin et al., 2010), CORBOB (Nikitin et al., 2009), OGEKAN (Nikulin et al., 2008) and TENBAP (Li et al., 1996)], although in the case of APOVUX it was specifically noted that the disorder model failed. A scatterplot of C—C distances versus C=C distances is shown in Fig. 2. The correlation between these two parameters is clear, such that for structures where there is no disorder present, or where the disorder model has been successfully implemented, the values of the C=C and C—C bond lengths are clearly different, ca 1.35 and 1.50 Å, respectively (e.g. OGEKAN), whereas for structures that demonstrate the disorder phenomenon these two bond lengths appear to be correlated and ultimately equilibrate to a value of ca 1.42 Å. The outlier point circled in Fig. 2 (QUGWUK; Basavaiah et al., 2001) is due to the incorrect assignment of the C-atom type when geometrically placing the H atoms; the 1.378 and 1.463 Å bond lengths should be assigned as C=C and C—C bonds, respectively, and not vice versa. The complete list of structures contained within this data set is available in the Supplementary materials.

In keeping with the findings above, the C=C and C—C bond lengths (C18=C19 and C18—C26, respectively) in (I) refined to values of 1.420 (3) and 1.443 (2) Å, respectively (shown as a square in Fig. 2, indicated with an arrow). A disorder model incorporating the two different components, with the sum of the occupancies constrained to unity, was attempted. However, in order for the refinement to converge successfully, the displacement parameters for the α-C atom C18 and its disordered component C18A had to be constrained as isotropic. The model converged, yielding occupancies of the two inden-2-yl components of 0.57 (2) and 0.43 (2). The resulting C=C and C—C bond lengths about C18/C18A were 1.29 (2)/1.52 (2) Å for component 1 and 1.35 (2)/1.60 (3) Å for component 2 (lower and upper triangles in Fig. 2, respectively). Further refinement cycles in which additional bond-length constraints were applied to all bonds about the α-C atom led to instability in the refinement. From this analysis it was concluded that the disorder model was insufficient and so the data presented here is based on the ordered model.

For the inden-2-yl moiety, the five-membered C18–C20/C25/C26 ring is planar, with C18—C19—C20—C25 and C20—C25—C26—C18 torsion angles of 1.36 (16) and −0.69 (16)°, respectively, whereas the five-membered C9–C11/C16/C17 ring of the inden-2-yl moiety adopts an envelope conformation or E form, with atom C9 displaced by 0.478 (2) Å from the mean plane defined by the other four atoms.

The absolute configuration of (I), viz. S, S and S at the chiral centres C9, C10 and C33, respectively, was determined by reference to the a priori knowledge of the chirality of the (S)-(-)-methylbenzylamine used in the salt-formation step and by anomalous dispersion methods (Flack, 1983). The determination of the absolute configuration of (I) by anomalous dispersion methods was likely to be challenging, given that the molecular formula and asymmetric unit contain only a single N and three O atoms. To maximize the likelihood of success, a full sphere of data was collected using Cu Kα radiation to a maximum resolution of 0.80 Å. A total of 25 532 reflections were collected, yielding a Flack parameter u for this structure of 0.00 (15) based on 2343 Friedel pairs. The value of u is slightly beyond the limit of enantiopure-sufficient distinguishing power (Flack & Bernadinelli, 1999, 2000), and for further confirmation of the absolute configuration a determination using Bayesian statistics on Bijvoet differences (Hooft et al., 2008), as implemented in the program PLATON (Spek, 2009), was performed. This gave probability values p3(ok), p3(twin) and p3(wrong) of 1.00, 0.000 and 0.000, respectively. The calculation was based on 2343 Bijvoet pairs. The absolute structure parameter and standard uncertainty calculated using this method was 0.11 (4). An improvement in the absolute structure parameter can be made using a Student t distribution rather than a Gaussian distribution (Hooft et al., 2010), giving −0.03 (13) for a ν parameter of 9.79. The overall p3 probability values calculated using this method remain unchanged at 1.000, 0.000 and 0.000.

The packing arrangement for (I) is best described as an infinite two-dimensional hydrogen-bond network in the (100) plane of the unit cell. The primary building block of this

---

**Figure 2**

A scatterplot of C=C versus C—C bond lengths for inden-2-yl fragments in the CSD. See the Comment for an explanation of the symbols.
network is the formation of an infinite chain of PH46 anions through a translational symmetry operation along the \( c \) axis of the unit cell. This interaction is formed by a single hydrogen bond from the hydroxy group of the substituted indenyl group, acting as donor, to a carbonyl O atom of the benzoate group, acting as acceptor \([O3—H3A···O2i = 2.7113 (14) \text{ Å}];\) see Table 1 for hydrogen-bond geometry and symmetry codes]. The hydrogen-bond network is extended by the formation of three further interactions linking the PH46 anion to the (1\( S \))-1-phenylethanaminium cation. These three interactions are formed by the \(-\text{NH}_3^+\) ammonium group acting as donor to O atoms of three different PH46 anions acting as acceptors. Two of these interactions bridge the infinite chain along the \( c \) axis to form an \( R_3^3(8) \) ring (Bernstein et al., 1995); \( N1—H1D—O2ii = 2.7991 (17) \text{ Å}. \) The \(-\text{NH}_3^+\) ammonium group of the cation makes a further donor interaction with the carbonyl O atom of a PH46 anion to form a larger overall two-dimensional network in the (100) plane; \( N1—H1D—O2iii = 2.7991 (17) \text{ Å}. \) Fig. 3 shows the four hydrogen-bond interactions described above. An overall view of the crystal packing down the \( a \) axis of the unit cell is shown in Fig. 4. All potential hydrogen-bond donors are utilized in the hydrogen-bonding arrangement, thus concurring with Etter’s first rule of hydrogen bonding for organic compounds, which states that all good H-atom donors and acceptors are used in hydrogen bonding (Etter, 1990).

**Experimental**

To an ethanol (7.5 ml) suspension of 4-[(1\( S \),2\( S \))-1-hydroxy-2,3-dihydro-1\( H \),1\( H’ \)-biinden]-2-yl]methyl]benzoic acid (PH46; 0.5 g, 1.31 mmol) was added (\( S \))-\( (\text{C}0\))-\( (\text{C}11\))-methylbenzylamine (0.2 ml, 1.5 mmol, 1.1 equivalents) portionwise. This reaction mixture was stirred for 2 h at 323 K and then left overnight at room temperature. Since no solid material was obtained, the solution was then concentrated under reduced pressure and diethyl ether (2 ml) was added to the flask. A white solid was immediately observed, which was further washed with diethyl ether (3\( \times \)4 ml). The organic solvent was removed using a Pasteur pipette and the remaining white solid was dried in a vacuum oven at 313 K (yield 0.56 g, 85%). Crystals of the salt, (I), were obtained by dissolving the crude material (ca 100 mg) in MeOH (3 ml) in a flat-bottomed sample tube, followed by the addition of diethyl ether (6 ml), which was added until the sample solution became slightly cloudy. The solution was filtered and placed in a dry-box at room temperature. A small amount of tetrahydrofuran (ca 0.5 ml) was added to the diethyl ether–methanol solution. After 5 d, colourless crystals of (I) were obtained (m.p. 467.2–467.9 K). \(^1\text{H NMR} (100 \text{ MHz}, d_6-\text{DMSO}); \delta 1.33 (d, 3H, \text{J} = 6.7 \text{ Hz}), 2.68 (d, 1H, \text{J} = 13.5 \text{ Hz}), 2.94, (d, 1H, \text{J} = 15.5 \text{ Hz}), 2.99 (d, 1H, \text{J} = 15.5 \text{ Hz}), 3.17 (d, 1H, \text{J} = 13.6 \text{ Hz}), 3.44 (d, 1H, \text{J} = 23.0 \text{ Hz}), 3.58 (d, 1H, \text{J} = 23.0 \text{ Hz}), 4.12 (q, 1H, \text{J} = 6.7 \text{ Hz}), 5.05 (s, 1H), 5.85 (br s, 1H), 6.41 (s, 1H), 6.86 (d, 2H, \text{J} = 8.2 \text{ Hz}), 7.08 (dt, 1H, \text{J} = 7.3, 1.3 \text{ Hz}), 7.14–7.44 (m, aromatic 12H), 7.65 (d, 2H, \text{J} = 8.2 \text{ Hz}).

**Figure 3**

A view of part of the crystal packing of (I). The figure shows the four hydrogen-bond interactions (thin lines) and the formation of the \( R_3^3(8) \) ring. [In the electronic version of the paper, molecules generated by the symmetry codes (i), (ii) and (iii) are represented by the colours green, red and blue, respectively, with hydrogen bonds shown as thin turquoise lines and incomplete hydrogen bonds as thin red lines.] For clarity, only H atoms attached to heteroatoms are shown. (The symmetry codes are as given in Table 1.)
Table 1
Hydrogen-bond geometry (Å, °).

| D—H—A      | D—H   | H—A   | D—A    | D—H—A  |
|-------------|--------|-------|--------|--------|
| O3—H3A···O2” | 0.85 (2) | 1.86 (2) | 2.7113 (14) | 177 (2) |
| N1—H1B—O3”  | 0.91 (2) | 2.05 (2) | 2.8799 (18) | 151 (2) |
| N1—H1C—O2”  | 0.92 (2) | 1.88 (2) | 2.7991 (17) | 178 (2) |
| N1—H1D—O1    | 0.91 (2) | 1.77 (2) | 2.6979 (16) | 174 (2) |

Symmetry codes: (i) x, y, z − 1; (ii) x, y, z + 1; (iii) −x + 2, y + 1/2, −z + 2.

Crystal data

C₆H₆N⁺·C₂₆H₂₁O₃⁻
Mᵣ = 503.61
Monoclinic, P₂₁
a = 11.0350 (3) Å
b = 10.1713 (3) Å
c = 11.8533 (3) Å
β = 93.678 (2)°
V = 1327.68 (6) Å³
Z = 2
Cu Kα radiation
μ = 0.63 mm⁻¹
T = 100 K

Data collection

Agilent SuperNova Dual
diffractometer, with Cu at zero and an Atlas detector
Absorption correction: multi-scan
(CrysAlis PRO; Agilent, 2011)
Tmax = 0.749, Tmin = 1.000

25532 measured reflections
5221 independent reflections
5157 reflections with I > 2σ(I)
Rint = 0.026

Refinement

H atoms treated by a mixture of independent and constrained refinement

Δρmax = 0.21 e Å⁻³
Δρmin = −0.21 e Å⁻³

Absolute structure: Flack (1983), with 2343 Friedel pairs
Flack parameter: 0.00 (15)

H atoms bonded to heteratoms were located in a difference map and refined. Other H atoms were positioned geometrically and refined using a riding model (including free rotation about the methyl C—C bond), with C—H = 0.95—0.99 Å and Uiso(H) = 1.5Ueq(C) for methyl groups or 1.2Ueq(C) otherwise.

Data collection: CrysAlis PRO (Agilent, 2011); cell refinement: CrysAlis PRO; data reduction: CrysAlis PRO; program(s) used to solve structure: SHELXTL (Sheldrick, 2008); program(s) used to refine structure: SHELXTL; molecular graphics: SHELXTL and Mercury (Macrae et al., 2008); software used to prepare material for publication: SHELXTL and Mercury.

The authors are grateful to Andrew Carr of Phamorphix for his assistance with the ¹H NMR assignment and to Professor A. L. Spek for helpful comments regarding the probability analysis.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3440). Services for accessing these data are described at the back of the journal.

References

Agilent (2011). CrysAlis PRO. Agilent Technologies, Yarnton, Oxfordshire, England.
Allen, F. H. (2002). Acta Cryst. B58, 380–388.
Basavaiah, D., Bakhadoss, M. & Reddy, G. J. (2001). Synthesis, pp. 919–923.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). Angew. Chem. Int. Ed. Engl. 34, 1555–1573.
Etter, M. C. (1990). Acc. Chem. Res. 23, 120–126.
Flack, H. D. (1983). Acta Cryst. A39, 876–881.
Flack, H. D. & Bernardinelli, G. (1999). Acta Cryst. A55, 908–915.
Flack, H. D. & Bernardinelli, G. (2008). J. Appl. Cryst. 32, 1143–1148.
Frankish, N., Farrell, R. & Sheridan, H. (2004). J. Pharm. Pharmacol. 56, 1423–1427.
Frankish, N. & Sheridan, H. J. (2012). J. Med. Chem. 55, 5497–5505.
Hirshfeld, F. L. (1976). Acta Cryst. A32, 239–244.
Hooft, R. W. W., Straver, L. H. & Spek, A. L. (2008). J. Appl. Cryst. 41, 96–103.
Hooft, R. W. W., Straver, L. H. & Spek, A. L. (2010). J. Appl. Cryst. 43, 665–668.
Li, S., Lundquist, K. & Stomberg, R. (1996). J. Chem. Crystallogr. 26, 287–291.
Lin, J. H. (1999). Adv. Drug. Deliver. Rev. 39, 33–49.
Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). J. Appl. Cryst. 41, 466–470.
Nikitin, K., Fleming, C., Muller-Bunz, H., Ortin, Y. & McGlinchey, M. J. (2010). Eur. J. Org. Chem. pp. 5203–5216.
Nikitin, K., Muller-Bunz, H., Ortin, Y. & McGlinchey, M. J. (2009). Chem. Eur. J. 15, 1836–1843.
Nikulin, M. V., Voskoboynikov, A. Z. & Suponitsky, K. Y. (2008). Acta Cryst. E64, o2317.
Scheper, M. A., Nikitakis, N. G., Chaisuparat, R., Montaner, S. & Saux, J. J. (2007). Neoplasia, 9, 192–199.
Sheldrick, G. M. (2008). Acta Cryst. A64, 112–122.
Sheridan, H., Frankish, N. & Farrell, R. (1999a). Planta Med. 65, 271–272.
Sheridan, H., Frankish, N. & Farrell, R. (1999b). Eur. J. Med. Chem. 34, 953–966.
Sheridan, H., Lemon, S., Frankish, N., Mc Ardle, P., Higgins, T., James, J. P. & Bhandroid, P. (1990). Eur. J. Med. Chem. 25, 603–608.
Sheridan, H., Walsh, J. J., Cogan, C., Jordan, M., McCabe, T., Passante, E. & Frankish, N. H. (2009). Bioorg. Med. Chem. Lett. 19, 5927–5930.
Sheridan, H., Walsh, J. J., Jordan, M., Cogan, C. & Frankish, N. (2009). Eur. J. Med. Chem. 44, 5018–5022.
Shiff, S. I., Qiao, L., Tsai, L. L. & Rigas, B. (1995). J. Clin. Invest. 96, 491–503.
Spek, A. L. (2009). Acta Cryst. D65, 148–155.
Vacca, J. P., Dorsey, B. D., Schleif, W. A., Levin, R. B., McDaniel, S. L., Darke, P. L., Zagay, J., Quintero, J. C., Blahy, O. M. & Roth, E. (1994). Proc. Natl Acad. Sci. USA, 91, 4096–4100.
supplementary materials

*Acta Cryst.* (2012). C**68**, o323–o326  [doi:10.1107/S0108270112031265]

(1S)-1-Phenylethanaminium 4-\{[(1S,2S)-1-hydroxy-2,3-dihydro-1H,1′H-[2,2′-biinden]-2-yl]methyl\}benzoate

Christopher S. Frampton, Tao Zhang, Gaia A. Scalabrino, Neil Frankish and Helen Sheridan

(1S)-1-Phenylethanaminium 4-\{[(1S,2S)-1-hydroxy-2,3-dihydro-1H,1′H-[2,2′-biinden]-2-yl]methyl\}benzoate

Crystal data

| Parameter         | Value           |
|-------------------|-----------------|
| C<sub>8</sub>H<sub>12</sub>N<sup>+</sup>-C<sub>26</sub>H<sub>21</sub>O<sub>3</sub><sup>−</sup> |                 |
| Mr                | 503.61          |
| Monoclinic, P<sub>2</sub><sub>1</sub> |                |
| a = 11.0350 (3) Å |                 |
| b = 10.1713 (3) Å |                 |
| c = 11.8533 (3) Å |                 |
| β = 93.678 (2)°  |                 |
| V = 1327.68 (6) Å<sup>3</sup> |             |
| Z = 2             |                 |
| F(000) = 536      |                 |

Data collection

| Parameter         | Value           |
|-------------------|-----------------|
| Agilent SuperNova Dual |              |
| diffractometer, with Cu at zero and an Atlas detector | |
| Radiation source: SuperNova (Cu) X-ray | |
| Source            |                 |
| Mirror monochromator |            |
| Detector resolution: 10.5598 pixels mm<sup>−1</sup> | |
| ω scans           |                 |
| Absorption correction: multi-scan | |
| (CrysAlis PRO; Agilent, 2011) |  |

Refinement

| Parameter         | Value           |
|-------------------|-----------------|
| Refinement on F<sup>2</sup> |              |
| Least-squares matrix: full |             |
| R(F<sup>2</sup> > 2σ(F<sup>2</sup>)) = 0.035 | |
| wR(F<sup>2</sup>) = 0.098 |            |
| S = 1.01          |                 |
| 5221 reflections  |                 |
| 362 parameters    |                 |
| 1 restraint       |                 |
| Primary atom site location: structure-invariant direct methods | |
| Secondary atom site location: difference Fourier map | |
| Hydrogen site location: inferred from neighbouring sites | |

H atoms treated by a mixture of independent and constrained refinement

| Parameter         | Value           |
|-------------------|-----------------|
| w = 1/[σ<sup>2</sup>(F<sub>c</sub>) + (0.075P)<sup>2</sup> + 0.250P] | |
| where P = (F<sub>c</sub><sup>2</sup> + 2F<sub>e</sub><sup>2</sup>)/3 | |
| (Δ/σ) < 0.001 |             |
| Δρ<sub>max</sub> = 0.21 e Å<sup>−3</sup> | |
| Δρ<sub>min</sub> = −0.21 e Å<sup>−3</sup> | |
| Extinction correction: SHELXTL (Sheldrick, 2008), F<sub>c</sub>' = kF<sub>c</sub>[1+0.001xF<sub>c</sub><sup>2</sup>/sin(2θ)]<sup>1/4</sup> | |
| Extinction coefficient: 0.0021 (4) | |
| Absolute structure: Flack (1983), with 2343 Friedel pairs | |
| Flack parameter: 0.00 (15) | |

supplementary materials
special details

Experimental. CrysAlisPro, Agilent Technologies, Version 1.171.35.19 (release 27-10-2011 CrysAlis171 .NET) (compiled Oct 27 2011,15:02:11) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

|    | x      | y      | z      | U(eq) |
|----|--------|--------|--------|-------|
| O1 | 0.97227(10) | 0.67327(12) | 0.83449(8) | 0.0226(2) |
| O2 | 0.92573(9) | 0.46529(11) | 0.87703(8) | 0.0191(2) |
| O3 | 0.89439(9) | 0.51048(11) | 0.09869(8) | 0.0182(2) |
| H3A| 0.9027(19) | 0.499(2)   | 0.029(2)   | 0.033(6)*  |
| C1 | 0.91707(13) | 0.37857(15) | 0.52630(12) | 0.0194(3) |
| H1A| 0.9223    | 0.2909   | 0.4994   | 0.023*    |
| C2 | 0.92760(13) | 0.40249(15) | 0.64190(12) | 0.0192(3) |
| H2A| 0.9402    | 0.3312   | 0.6931   | 0.023*    |
| C3 | 0.91987(11) | 0.52948(15) | 0.68328(11) | 0.0156(3) |
| C4 | 0.94029(12) | 0.55850(15) | 0.80808(11) | 0.0158(3) |
| C5 | 0.89799(13) | 0.63239(15) | 0.60755(11) | 0.0185(3) |
| H5A| 0.8904    | 0.7196   | 0.6349   | 0.022*    |
| C6 | 0.88715(13) | 0.60794(15) | 0.49189(12) | 0.0193(3) |
| H6A| 0.8714    | 0.6790   | 0.4411   | 0.023*    |
| C7 | 0.89896(11) | 0.48130(15) | 0.44897(11) | 0.0161(3) |
| C8 | 0.90019(12) | 0.45817(16) | 0.32278(10) | 0.0174(3) |
| H8A| 0.9452    | 0.3758   | 0.3104   | 0.021*    |
| H8B| 0.9459    | 0.5308   | 0.2895   | 0.021*    |
| C9 | 0.77439(12) | 0.44829(15) | 0.25795(11) | 0.0161(3) |
| C10| 0.79016(12) | 0.43611(15) | 0.12766(11) | 0.0168(3) |
| H10A| 0.7962   | 0.3421   | 0.1039   | 0.020*    |
| C11| 0.67726(12) | 0.50009(15) | 0.07553(11) | 0.0181(3) |
| C12| 0.63315(13) | 0.49669(17) | -0.03744(12) | 0.0219(3) |
| H12A| 0.6692  | 0.4411   | -0.0904  | 0.026*    |
| C13| 0.53492(14) | 0.57693(18) | -0.07056(13) | 0.0257(3) |
| C13A| 0.5038  | 0.5765   | -0.1472  | 0.031*    |
| C14| 0.48202(13) | 0.65749(18) | 0.00710(15) | 0.0275(3) |
| C14A| 0.4147  | 0.7111   | -0.0169  | 0.033*    |
| C15| 0.52649(13) | 0.66076(17) | 0.12012(14) | 0.0238(3) |
| H15A| 0.4900  | 0.7157   | 0.1732   | 0.029*    |
| C16| 0.62537(12) | 0.58175(15) | 0.15320(12) | 0.0185(3) |
| C17| 0.69704(13) | 0.57468(15) | 0.26644(12) | 0.0185(3) |
| H17A| 0.6422  | 0.5681   | 0.3291   | 0.022*    |
| H17B| 0.7495  | 0.6530   | 0.2786   | 0.022*    |
| C18| 0.70480(12) | 0.32897(15) | 0.29625(11) | 0.0166(3) |
| C19| 0.75503(14) | 0.20146(16) | 0.31348(12) | 0.0226(3) |
| H19A| 0.8364  | 0.1762   | 0.3031   | 0.027*    |
| C20| 0.65735(13) | 0.11507(16) | 0.35061(11) | 0.0205(3) |
| C21| 0.65690(16) | -0.01722(18) | 0.37918(13) | 0.0278(3) |
| H21A| 0.7294  | -0.0677  | 0.3798   | 0.033*    |
| C22| 0.54745(18) | -0.07482(19) | 0.40716(14) | 0.0320(4) |
supplementary materials

| Atomic coordinates (Å) |          |          |          |          |          |          |
|------------------------|----------|----------|----------|----------|----------|----------|
| H22A                   | 0.5454   | −0.1657  | 0.4256   | 0.038*   |          |          |
| C23                    | 0.44189 (16) | −0.0006 (2) | 0.40821 (14) | 0.0318 (4) |          |          |
| H23A                   | 0.3683   | −0.0413  | 0.4270   | 0.038*   |          |          |
| C24                    | 0.44272 (14) | 0.13288 (18) | 0.38206 (13) | 0.0269 (3) |          |          |
| H24A                   | 0.3709   | 0.1840   | 0.3843   | 0.032*   |          |          |
| C25                    | 0.55085 (14) | 0.18992 (16) | 0.35255 (11) | 0.0210 (3) |          |          |
| C26                    | 0.57753 (14) | 0.32620 (17) | 0.31758 (13) | 0.0239 (3) |          |          |
| H26A                   | 0.5273   | 0.3500   | 0.2484   | 0.029*   |          |          |
| H26B                   | 0.5602   | 0.3890   | 0.3783   | 0.029*   |          |          |
| N1                     | 0.90975 (11) | 0.78051 (13) | 1.02795 (10) | 0.0189 (3) |          |          |
| H1B                    | 0.9082 (19) | 0.710 (2) | 1.0743 (19) | 0.025 (5)* |          |          |
| H1C                    | 0.966 (2) | 0.840 (2) | 1.0589 (18) | 0.028 (5)* |          |          |
| H1D                    | 0.933 (2) | 0.749 (2) | 0.961 (2) | 0.031 (5)* |          |          |
| C27                    | 0.81467 (13) | 1.06674 (17) | 0.92266 (13) | 0.0221 (3) |          |          |
| H27A                   | 0.8446   | 1.0993   | 0.9942   | 0.026*   |          |          |
| C28                    | 0.80522 (14) | 1.15072 (17) | 0.82987 (14) | 0.0253 (3) |          |          |
| H28A                   | 0.8271   | 1.2406   | 0.8386   | 0.030*   |          |          |
| C29                    | 0.76376 (14) | 1.10320 (18) | 0.72436 (14) | 0.0273 (3) |          |          |
| H29A                   | 0.7576   | 1.1604   | 0.6609   | 0.033*   |          |          |
| C30                    | 0.73157 (15) | 0.9727 (2) | 0.71210 (13) | 0.0303 (4) |          |          |
| H30A                   | 0.7041   | 0.9399   | 0.6399   | 0.036*   |          |          |
| C31                    | 0.73922 (14) | 0.88904 (18) | 0.80497 (13) | 0.0253 (3) |          |          |
| H31A                   | 0.7161   | 0.7995   | 0.7961   | 0.030*   |          |          |
| C32                    | 0.78069 (12) | 0.93597 (16) | 0.91144 (12) | 0.0198 (3) |          |          |
| C33                    | 0.78543 (13) | 0.84192 (16) | 1.01074 (12) | 0.0200 (3) |          |          |
| H33A                   | 0.7257   | 0.7699   | 0.9927   | 0.024*   |          |          |
| C34                    | 0.75416 (15) | 0.90403 (17) | 1.12179 (13) | 0.0256 (3) |          |          |
| H34A                   | 0.6714   | 0.9394   | 1.1140   | 0.038*   |          |          |
| H34B                   | 0.8114   | 0.9754   | 1.1413   | 0.038*   |          |          |
| H34C                   | 0.7595   | 0.8374   | 1.1816   | 0.038*   |          |          |

Atomic displacement parameters (Å²)

|        | U¹¹ | U¹² | U¹³ | U²² | U²³ | U³³ |
|--------|-----|-----|-----|-----|-----|-----|
| O1     | 0.0316 (5) | 0.0215 (6) | 0.0148 (4) | −0.0046 (4) | 0.0014 (4) | −0.0027 (4) |
| O2     | 0.0244 (5) | 0.0211 (6) | 0.0119 (4) | 0.0015 (4) | 0.0020 (3) | 0.0013 (4) |
| O3     | 0.0196 (5) | 0.0244 (6) | 0.0107 (4) | −0.0016 (4) | 0.0024 (3) | −0.0004 (4) |
| C1     | 0.0247 (7) | 0.0182 (7) | 0.0154 (7) | 0.0024 (6) | 0.0016 (5) | −0.0028 (5) |
| C2     | 0.0256 (7) | 0.0192 (8) | 0.0130 (6) | 0.0025 (6) | 0.0021 (5) | 0.0036 (5) |
| C3     | 0.0147 (6) | 0.0202 (7) | 0.0119 (6) | −0.0012 (5) | 0.0010 (4) | −0.0004 (5) |
| C4     | 0.0155 (6) | 0.0199 (7) | 0.0121 (6) | 0.0017 (5) | 0.0015 (4) | −0.0004 (5) |
| C5     | 0.0224 (6) | 0.0174 (7) | 0.0153 (6) | −0.0019 (5) | −0.0010 (5) | −0.0007 (5) |
| C6     | 0.0244 (7) | 0.0183 (7) | 0.0147 (6) | −0.0030 (5) | −0.0036 (5) | 0.0037 (5) |
| C7     | 0.0140 (5) | 0.0218 (8) | 0.0123 (6) | −0.0024 (5) | 0.0006 (4) | 0.0000 (5) |
| C8     | 0.0169 (6) | 0.0230 (8) | 0.0126 (6) | −0.0015 (5) | 0.0004 (5) | 0.0010 (5) |
| C9     | 0.0182 (6) | 0.0191 (7) | 0.0110 (5) | −0.0007 (5) | 0.0011 (5) | −0.0005 (5) |
| C10    | 0.0195 (6) | 0.0201 (7) | 0.0109 (6) | −0.0022 (5) | 0.0008 (5) | −0.0004 (5) |
| C11    | 0.0188 (6) | 0.0191 (7) | 0.0163 (6) | −0.0042 (5) | 0.0002 (5) | 0.0022 (5) |
| C12    | 0.0224 (7) | 0.0258 (8) | 0.0170 (6) | −0.0065 (6) | −0.0021 (5) | 0.0016 (6) |
| C13    | 0.0229 (7) | 0.0319 (9) | 0.0212 (7) | −0.0076 (6) | −0.0074 (5) | 0.0068 (6) |

Acta Cryst. (2012). C68, o323–o326
supplementary materials

Geometric parameters (Å, °)

| Atoms | Distance 1 | Distance 2 | Distance 3 | Distance 4 | Distance 5 | Distance 6 |
|-------|------------|------------|------------|------------|------------|------------|
| O1—C4 | 1.2534 (19) | C18—C26 | 1.443 (2) |
| O2—C4 | 1.2686 (18) | C19—C20 | 1.479 (2) |
| O3—C10 | 1.4365 (17) | C20—C21 | 1.390 (2) |
| O3—H3A | 0.85 (2) | C21—C22 | 1.396 (2) |
| C1—C2 | 1.389 (2) | C22—C23 | 1.386 (2) |
| C1—C7 | 1.396 (2) | C23—C24 | 1.390 (2) |
| C1—H1A | 0.9500 | C24—C25 | 1.391 (19) |
| C2—C3 | 1.386 (2) | C25—C26 | 1.5463 (17) |
| C2—H2A | 0.9500 | C26—H26A | 1.5092 (19) |
| C3—C5 | 1.390 (2) | C26—H26B | 0.9900 |
| C3—C4 | 1.5111 (17) | C26—H26C | 0.9900 |
| C5—C6 | 1.3910 (19) | C27—C28 | 1.5701 (17) |
| C5—H5A | 0.9500 | C27—H27A | 1.391 (2) |
| C6—C7 | 1.394 (2) | C27—H27B | 0.9500 |
| C6—H6A | 0.9500 | C28—C29 | 1.391 (2) |
| C7—C8 | 1.5152 (17) | C28—H28A | 0.9500 |
| C8—C9 | 1.5463 (17) | N1—C33 | 1.5092 (19) |
| C8—H8A | 0.9900 | N1—H1B | 0.91 (2) |
| C8—H8B | 0.9900 | N1—H1C | 0.92 (2) |
| C9—C18 | 1.521 (2) | N1—H1D | 0.91 (2) |
| C9—C17 | 1.550 (2) | C27—C32 | 1.386 (2) |
| C9—C10 | 1.5701 (17) | C27—C28 | 1.391 (2) |
| C10—C11 | 1.5029 (19) | C27—H27A | 0.9500 |
| C10—H10A | 1.0000 | C28—C29 | 1.391 (2) |
| C11—C16 | 1.390 (2) | C28—H28A | 0.9500 |

Acta Cryst. (2012). C68, o323–o326
supplementary materials

| Bond                  | Distance (Å)     |
|-----------------------|------------------|
| C11—C12               | 1.3956 (19)      |
| C12—C13               | 1.393 (2)        |
| C12—H12A              | 0.9500           |
| C13—C14               | 1.389 (3)        |
| C13—H13A              | 0.9500           |
| C14—C15               | 1.397 (2)        |
| C14—H14A              | 0.9500           |
| C15—C16               | 1.391 (2)        |
| C15—H15A              | 0.9500           |
| C16—C17               | 1.5153 (19)      |
| C17—H17A              | 0.9900           |
| C17—H17B              | 0.9900           |
| C18—C19               | 1.420 (2)        |
| C10—O3—H3A            | 107.5 (15)       |
| C2—C1—C7              | 121.07 (14)      |
| C2—C1—H1A             | 119.5            |
| C7—C1—H1A             | 119.5            |
| C3—C2—C1              | 120.60 (13)      |
| C3—C2—H2A             | 119.7            |
| C1—C2—H2A             | 119.7            |
| C2—C3—C5              | 119.03 (12)      |
| C2—C3—C4              | 121.31 (13)      |
| C5—C3—C4              | 119.60 (13)      |
| O1—C4—O2              | 125.47 (12)      |
| O1—C4—C3              | 116.64 (12)      |
| O2—C4—C3              | 117.87 (13)      |
| C3—C5—C6              | 120.15 (14)      |
| C3—C5—H5A             | 119.9            |
| C6—C5—H5A             | 119.9            |
| C5—C6—C7              | 121.38 (14)      |
| C5—C6—H6A             | 119.3            |
| C7—C6—H6A             | 119.3            |
| C6—C7—C1              | 117.70 (12)      |
| C6—C7—C8              | 120.71 (13)      |
| C1—C7—C8              | 121.47 (13)      |
| C7—C8—C9              | 115.85 (11)      |
| C7—C8—H8A             | 108.3            |
| C9—C8—H8A             | 108.3            |
| C7—C8—H8B             | 108.3            |
| C9—C8—H8B             | 108.3            |
| H8A—C8—H8B            | 107.4            |
| C18—C9—C8             | 110.97 (11)      |
| C18—C9—C17            | 110.60 (11)      |
| C8—C9—C17             | 113.23 (12)      |
| C18—C9—C10            | 108.70 (11)      |
| C8—C9—C10             | 109.95 (10)      |
| C17—C9—C10            | 103.03 (11)      |
| O3—C10—C11            | 109.20 (12)      |

Acta Cryst. (2012). C68, o323–o326
| Bond/Angle | Value (°/°) | Bond/Angle | Value (°/°) |
|------------|------------|------------|------------|
| C3—C10—C9 | 109.55 (11) | C32—C27—C28 | 120.48 (15) |
| C11—C10—C9 | 103.24 (11) | C32—C27—H27A | 119.8 |
| O3—C10—H10A | 111.5 | C28—C27—H27A | 119.8 |
| C11—C10—H10A | 111.5 | C29—C28—C27 | 120.09 (16) |
| C9—C10—H10A | 111.5 | C29—C28—H28A | 120.0 |
| C16—C11—C12 | 121.13 (14) | C27—C28—H28A | 120.0 |
| C16—C11—C10 | 110.62 (12) | C30—C29—C28 | 119.79 (15) |
| C12—C11—C10 | 127.79 (14) | C30—C29—H29A | 120.1 |
| C13—C12—C11 | 118.24 (15) | C28—C29—H29A | 120.1 |
| C13—C12—H12A | 120.9 | C29—C30—C31 | 120.25 (15) |
| C11—C12—H12A | 120.9 | C29—C30—H30A | 119.9 |
| C14—C13—C12 | 120.76 (14) | C31—C30—H30A | 119.9 |
| C14—C13—H13A | 119.6 | C30—C31—C32 | 120.36 (16) |
| C12—C13—H13A | 119.6 | C30—C31—H31A | 119.8 |
| C13—C14—C15 | 120.86 (15) | C32—C31—H33A | 119.8 |
| C13—C14—H14A | 119.6 | C27—C32—C31 | 119.01 (15) |
| C15—C14—H14A | 119.6 | C27—C32—C33 | 122.40 (13) |
| C16—C15—C14 | 118.51 (15) | C31—C32—C33 | 118.59 (14) |
| C16—C15—H15A | 120.7 | N1—C33—C32 | 110.62 (11) |
| C14—C15—H15A | 120.7 | N1—C33—C34 | 108.06 (12) |
| C11—C16—C15 | 120.49 (13) | C32—C33—C34 | 114.33 (13) |
| C11—C16—C17 | 110.15 (12) | N1—C33—H33A | 107.9 |
| C15—C16—C17 | 129.23 (14) | C32—C33—H33A | 107.9 |
| C16—C17—C9 | 103.90 (12) | C34—C33—H33A | 107.9 |
| C16—C17—H17A | 111.0 | C33—C34—H34A | 109.5 |
| C9—C17—H17A | 111.0 | C33—C34—H34B | 109.5 |
| C16—C17—H17B | 111.0 | H34A—C34—H34B | 109.5 |
| C9—C17—H17B | 111.0 | C33—C34—H34C | 109.5 |
| H17A—C17—H17B | 109.0 | H34A—C34—H34C | 109.5 |
| C19—C18—C26 | 109.40 (13) | H34B—C34—H34C | 109.5 |
| C7—C1—C2—C3 | 0.2 (2) | C15—C16—C17—C9 | 167.53 (15) |
| C1—C2—C3—C5 | 1.8 (2) | C18—C9—C17—C16 | −88.29 (13) |
| C1—C2—C3—C4 | −175.44 (12) | C8—C9—C17—C16 | 146.44 (11) |
| C2—C3—C4—O1 | 156.52 (14) | C10—C9—C17—C16 | 27.72 (13) |
| C5—C3—C4—O1 | −20.69 (18) | C8—C9—C18—C19 | −44.49 (17) |
| C2—C3—C4—O2 | −22.41 (19) | C17—C9—C18—C19 | −171.03 (12) |
| C5—C3—C4—O2 | 160.38 (13) | C10—C9—C18—C19 | 76.54 (16) |
| C2—C3—C5—C6 | −1.6 (2) | C8—C9—C18—C26 | 137.40 (13) |
| C4—C3—C5—C6 | 175.68 (12) | C10—C9—C18—C26 | 10.86 (18) |
| C3—C5—C6—C7 | −0.6 (2) | C10—C9—C18—C26 | −101.57 (15) |
| C5—C6—C7—C1 | 2.6 (2) | C26—C18—C19—C20 | −1.81 (15) |
| C5—C6—C7—C8 | −173.49 (13) | C9—C18—C19—C20 | 179.82 (12) |
| C2—C1—C7—C6 | −2.4 (2) | C18—C19—C20—C21 | −179.67 (14) |
| C2—C1—C7—C8 | 173.66 (13) | C18—C19—C20—C25 | 1.36 (16) |
| C6—C7—C8—C9 | −83.83 (17) | C25—C20—C21—C22 | 1.6 (2) |
| C1—C7—C8—C9 | 100.22 (16) | C19—C20—C21—C22 | −177.31 (14) |
| C7—C8—C9—C18 | −64.37 (17) | C20—C21—C22—C23 | −1.1 (2) |
| C7—C8—C9—C17 | 60.70 (16) | C21—C22—C23—C24 | −0.4 (3) |
C7—C8—C9—C10 175.34 (13) C22—C23—C24—C25 1.3 (2)
C18—C9—C10—O3 −155.39 (11) C23—C24—C25—C20 −0.9 (2)
C8—C9—C10—C11 −33.73 (16) C23—C24—C25—C26 177.79 (15)
C17—C9—C10—O3 87.25 (13) C21—C20—C25—C24 −0.6 (2)
C18—C9—C10—C11 88.37 (13) C19—C20—C25—C24 178.51 (13)
C8—C9—C10—C11 −149.97 (12) C21—C20—C25—C26 −179.50 (13)
C17—C9—C10—C11 −28.99 (14) C19—C20—C25—C26 −0.40 (16)
O3—C10—C11—C16 −96.36 (13) C19—C18—C26—C25 1.56 (15)
C9—C10—C11—C16 20.12 (16) C9—C18—C26—C25 179.92 (12)
O3—C10—C11—C12 75.84 (19) C24—C25—C26—C18 −179.46 (15)
C9—C10—C11—C12 −167.68 (15) C20—C25—C26—C18 −0.69 (16)
C16—C11—C12—C13 −0.4 (2) C32—C27—C28—C29 −1.3 (2)
C10—C11—C12—C13 −171.84 (14) C27—C28—C29—C30 0.3 (2)
C11—C12—C13—C14 −0.4 (2) C28—C29—C30—C31 0.7 (3)
C12—C13—C14—C15 0.4 (2) C29—C30—C31—C32 −0.6 (3)
C13—C14—C15—C16 0.2 (2) C28—C27—C32—C31 1.3 (2)
C12—C11—C16—C15 1.0 (2) C28—C27—C32—C33 −177.95 (13)
C10—C11—C16—C15 173.84 (13) C30—C31—C32—C27 −0.4 (2)
C12—C11—C16—C17 −175.21 (13) C30—C31—C32—C33 178.92 (14)
C10—C11—C16—C17 −2.40 (17) C27—C32—C33—N1 −86.92 (17)
C14—C15—C16—C11 −0.9 (2) C31—C32—C33—N1 93.78 (15)
C14—C15—C16—C17 174.50 (15) C27—C32—C33—C34 35.32 (19)
C11—C16—C17—C9 −16.65 (15) C31—C32—C33—C34 −143.97 (14)

Hydrogen-bond geometry (Å, º)

| D—H···A  | D—H  | H···A  | D···A  | D—H···A |
|---------|------|-------|--------|---------|
| O3—H3A···O2i | 0.85 (2) | 1.86 (2) | 2.7113 (14) | 177 (2) |
| N1—H1B···O3ii | 0.91 (2) | 2.05 (2) | 2.8799 (18) | 151 (2) |
| N1—H1C···O2iii | 0.92 (2) | 1.88 (2) | 2.7991 (17) | 178 (2) |
| N1—H1D···O1  | 0.91 (2) | 1.77 (2) | 2.6697 (16) | 174 (2) |

Symmetry codes: (i) x, y, z−1; (ii) x, y, z+1; (iii) −x+2, y+1/2, −z+2.