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# Nobiletin: a citrus flavonoid displaying potent physiological activity

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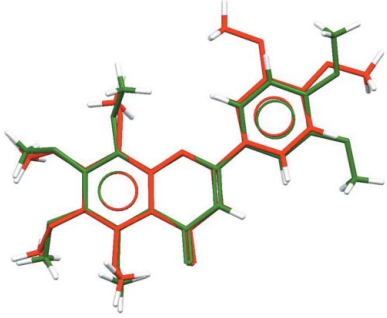
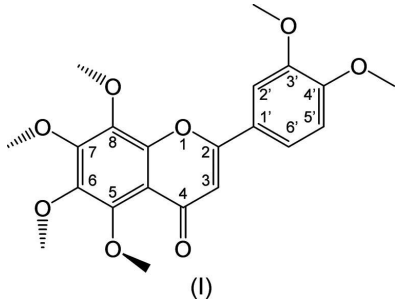
Nobiletin [systematic name: 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxy-4*H*-chromen-4-one; $C_{21}H_{22}O_8$] is a flavonoid found in citrus peels, and has been reported to show a wide range of physiological properties, including anti-inflammatory, anticancer and antidementia activities. We have solved the crystal structure of nobiletin, which revealed that the chromene and arene rings of its flavone moiety, as well as the two methoxy groups bound to its arene ring, were coplanar. In contrast, the C atoms of the four methoxy groups bound to the chromene ring are out of the plane, making the molecule conformationally chiral. A comparison of the crystal structures of nobiletin revealed that it could adopt a variety of different conformations through rotation of the covalent bond between the chromene and arene rings, and the orientations of methoxy groups bound to the chromene ring.

## 1. Introduction

Nobiletin, (I), is a flavonoid compound that can be found in large quantities in citrus peels. Nobiletin and its metabolites (Lai *et al.*, 2008; Li *et al.*, 2014) have been reported to possess a variety of interesting physiological properties, including anti-inflammatory (Lin *et al.*, 2003), anticancer (Kunimasa *et al.*, 2010), anti-apoptosis (Akao *et al.*, 2008), antidementia (Nagase *et al.*, 2005) and neuroprotective (Yasuda *et al.*, 2014) activities. Based on its potent physiological activities, nobiletin has become an attractive candidate for use as a therapeutic agent. The physiological activities of nobiletin have been attributed to its ability to modulate cell-signaling pathways, including cAMP response elements (Nagase *et al.*, 2005) and NF-$\kappa$B (Cui *et al.*, 2010), as well as its ability to alter the expression of specific genes (Nemoto *et al.*, 2013; Kimura *et al.*, 2014). However, the molecular mechanisms of nobiletin are not clear because the target receptor molecules to which this compound might bind have not yet been definitively identified. Investigations to identify the receptors are currently underway.





(I)

The three-dimensional molecular structure of nobiletin had been identified as a complex structure with a porous material

using the 'crystalline sponge' method (Inokuma *et al.*, 2013). However, the quality of the electron-density map for nobiletin did not appear to be satisfactory in terms of its atomic resolution, probably because of its high thermal vibrations, disorder or the low occupancy levels of the nobiletin molecules in the complex structure. We have determined a single-crystal structure of nobiletin and compared the differences in the molecular conformations of nobiletin in a variety of different crystal-packing environments.

## 2. Experimental

### 2.1. Synthesis, crystallization and PXRD analysis

Nobiletin was synthesized according to a previously reported procedure and crystallized from aqueous methanol to give the desired material as fine needles (Asakawa *et al.*, 2011). Nobiletin was dissolved in ethyl acetate and the resulting solution was filtered through a 0.45 µm membrane filter. A sample of the filtered solution (500 µl) was then poured into a Petri dish with a diameter of 15 mm. The solution was allowed to evaporate slowly at 298 K over a period of 2 d to give fine white crystals with a columnar shape. The crystals were analyzed by powder X-ray diffraction (PXRD) using a Rigaku Mini Flex II X-ray diffractometer. The PXRD pattern of the crystals prepared from ethyl acetate was identical to that of the crystals prepared from an aqueous methanol solution. This result confirmed that the crystal form of nobiletin had not changed during the recrystallization process.

### 2.2. Refinement and twinning

Crystal data, data collection and structure refinement details are summarized in Table 1. The diffraction images indicated that the crystal used for the data-collection process was a twin crystal made of two separate crystals, and that the *c* axes of the two crystals were almost parallel. Given that the diffraction spots from each crystal were well separated in the diffraction images, it was possible to collect diffraction data from one of the crystals that diffracted more than $\sin\theta/\lambda = 0.625$ Å$^{-1}$. During the refinement process, the H atoms were located in a difference Fourier map and were constrained as riding, with $U_{iso}(H) = 1.2U_{eq}(C)$.

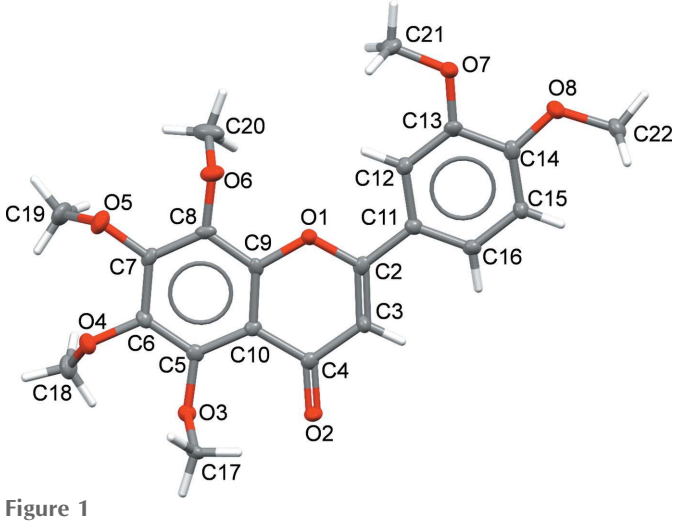



**Figure 1**
The molecular structure of nobiletin, showing the atom-numbering scheme. C, H and O atoms are shown in grey, white and red, respectively. Displacement ellipsoids are drawn at the 50% probability level.

**Table 1**
Experimental details.

| | |
|---|---|
| Crystal data | |
| Chemical formula | $C_{21}H_{22}O_8$ |
| $M_r$ | 402.38 |
| Crystal system, space group | Orthorhombic, $P2_12_12_1$ |
| Temperature (K) | 100 |
| $a, b, c$ (Å) | 19.3239 (17), 22.921 (2), 4.1385 (4) |
| $V$ (Å$^3$) | 1833.0 (3) |
| $Z$ | 4 |
| Radiation type | Synchrotron. SPring-8 BL02B1, $\lambda$ = 0.70041 Å |
| $\mu$ (mm$^{-1}$) | 0.11 |
| Crystal size (mm) | 0.50 × 0.02 × 0.01 |
| Data collection | |
| Diffractometer | Rigaku Mercury2 CCD four-circle diffractometer |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 13177, 4894, 4091 |
| $R_{int}$ | 0.043 |
| $(\sin\theta/\lambda)_{max}$ (Å$^{-1}$) | 0.705 |
| Refinement | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ | 0.065, 0.192, 1.29 |
| No. of reflections | 4894 |
| No. of parameters | 268 |
| H-atom treatment | H-atom parameters constrained |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å$^{-3}$) | 0.42, −0.29 |
| Absolute structure | An arbitrary choice of enantiomer was made |

Computer programs: *RAPID-AUTO* (Rigaku, 2010), *SHELXT* (Sheldrick, 2015*a*), *SHELXL2014* (Sheldrick, 2015*b*), *shelXle* (Hübschle *et al.*, 2011), *Mercury* (Macrae *et al.*, 2008) and *publCIF* (Westrip, 2010).

## 3. Results and discussion

The X-ray crystal structure of nobiletin, (I), solved in the current study revealed that the asymmetric unit contains one molecule (Fig. 1). Furthermore, no voids were identified in the crystal structure that could accommodate solvent molecules, confirming that this crystal had been isolated in the unsolvated form. The planes of the chromene and arene rings of nobiletin are almost parallel, as exemplified by the torsion angle of the covalent bond between the chromene and arene rings (O1—C2—C11—C12) of −0.6 (5)°. The C atoms of the two methoxy groups at the 3′- and 4′-positions of the arene ring (see Scheme) are also located in the plane of the flavone. In contrast, the C atoms of the methoxy moieties on the chromene ring are not in the same plane as the flavone. The C5 methyl group projects forwards away from the plane of the chromene ring, whilst the C6, C7 and C8 methyl groups project backwards away from the plane of the ring. The molecular structure of nobiletin in this crystal is therefore chiral because of its conformational characteristics, despite the fact that nobiletin does not contain an asymmetric C atom. However, it was not possible to determine which enantiomorph was

Table 2
Close C—H···O contacts (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| C22—H22$B$···O2$^{i}$ | 0.98 | 2.70 | 3.479 (5) | 137 |
| C17—H17$B$···O3$^{ii}$ | 0.98 | 2.48 | 3.457 (5) | 172 |
| C18—H18$A$···O4$^{iii}$ | 0.98 | 2.66 | 3.193 (6) | 114 |
| C20—H20$B$···O6$^{iii}$ | 0.98 | 2.49 | 3.450 (6) | 165 |
| C22—H22$A$···O8$^{iii}$ | 0.98 | 2.66 | 3.584 (6) | 158 |
| C19—H19$B$···O7$^{iv}$ | 0.98 | 2.65 | 3.346 (5) | 128 |
| C19—H19$B$···O8$^{iv}$ | 0.98 | 2.43 | 3.292 (5) | 147 |

Symmetry codes: (i) $-x+\frac{3}{2}, -y+1, z+\frac{1}{2}$; (ii) $x, y, z+1$; (iii) $x, y, z-1$; (iv) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$.

responsible for this crystal based on the differences in the intensities of the Friedel pair reflections. This could be attributable to the scattering of the C and O atoms of the anomalous imaginary part being too small to be detected at the wavelength used for the data collection in this study [*i.e.* 0.7004 (1) Å]. The crystals grown from an ethyl acetate solution may therefore have been a mixture of two enantiomorphic forms, as is often the case for the crystals of organic compounds (Koizumi *et al.*, 2008).

The plane of best fit for the flavone ring of nobiletin forms an angle of 31° with the *ab* plane and is stacked along the *c* axis (Fig. 2). The distance between the planes of the flavone rings, as represented by the distance between atom C13 and atom C15 at ($x$, $y$, $z+1$), is 3.497 (7) Å. Table 2 shows details of the close intermolecular contacts less than the sum of the van der Waals radii between the H atoms of the methoxy groups and the O atoms. Carbonyl atom O2$^{i}$ (see Table 2 for geometry details and symmetry code), which is capable of forming a strong hydrogen bond as a hydrogen-bond acceptor, is in contact with atom H22$B$ of the C22 methyl group. The H22$B$···O2$^{i}$ and C22···O2$^{i}$ distances are shorter than the average values reported for H···O and C···O contacts involving methyl groups and carbonyl O atoms [2.761 (6) and 3.590 (7) Å, respectively; Steiner & Desiraju, 1998]. The C22—H22$B$···O2$^{i}$ angle is greater than 100°, which is the value needed for a C—H group to form a hydrogen-bonding interaction (Jensen *et al.*, 2003). The geometrical characteristics of this structure suggest that the C22—H22$B$···O2$^{i}$ contacts possess a weak hydrogen-bonding characteristic. All of the other close contacts between the H and O atoms of the methoxy groups have C—H···O angles greater than 100°, which implies that these contacts also possess some hydrogen-bonding characteristics (Pingali *et al.*, 2015). However, these contacts are weaker than C22—H22$B$···O2$^{i}$ because a carbonyl O atom is a better hydrogen-bond acceptor than a methoxy O atom.

Fig. 3 shows the superimposition of the molecular structure of nobiletin determined in this study (denoted NOB-1) on the molecular structure determined using the 'crystalline sponge' method (denoted NOB-2). The O1—C2—C15—C16 torsion angle in NOB-2 is −172 (2)°, which shows that the arene ring of the NOB-2 structure is almost flipped compared with that of the NOB-1 structure. Unlike the NOB-1 structure, the arene and chromene rings of the NOB-2 structure are not coplanar and are distorted by approximately 8°. The other main difference between the two structures is the conformation of the methoxy groups bound to the chromene ring. The C20 methyl group in the NOB-1 structure extends towards the same side of the chromene ring as the C18 and C19 methyl groups, whereas the C20 methyl in the NOB-2 structure extends towards the opposite side of the ring. The superimposition of the two structures also suggests that it would not be possible to pack the NOB-1 structure into the cavities of the crystalline sponge in the same way as the NOB-2 structure because of the steric hindrance between the methoxy groups of nobiletin and the sponge. Close contacts less than van der Waals distances were found between the C20 methyl group of the superimposed NOB1 structure and a pyridine ring of the

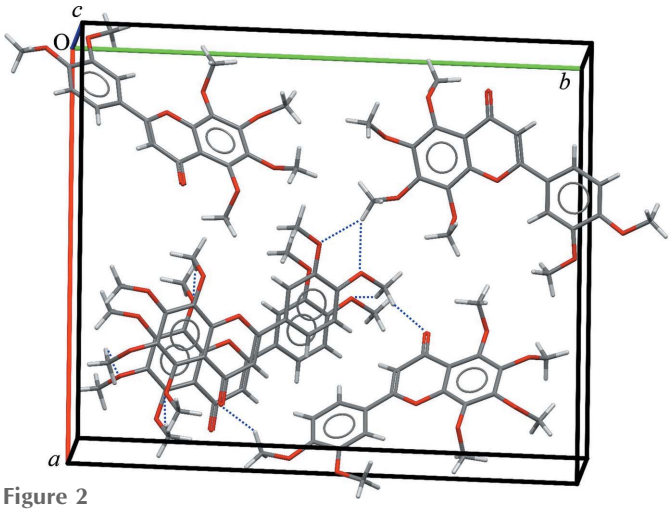



Figure 2
The crystal packing of nobiletin. Close C—H···O contacts listed in Table 2 are shown in blue dotted lines.

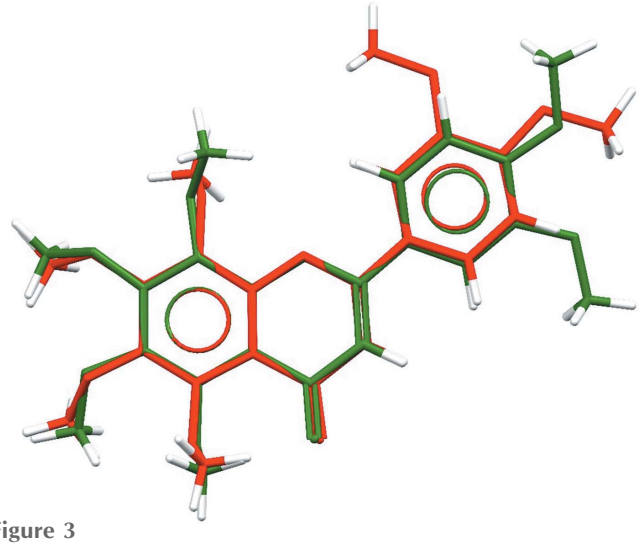


Figure 3
Comparison of the different conformational structures of nobiletin. The non-H atoms of NOB1 and NOB2 are shown in red and green, respectively. The H atoms in both structures are shown in white. The crystal structure obtained by the sponge method contained a pair of enantiomers of nobiletin in the crystal lattice with the space group *C*2/*c*, and one of these enantiomers is shown in the figure.

sponge, and between the C21 methyl group of the NOB1 structure and an I atom bound to a Zn atom of the sponge. In solution, nobiletin may be in equilibrium with a variety of different conformers, which could differ, at least, in the conformation of the methoxy groups bound to the chromene ring and the torsion angle around the covalent bond between the chromene and arene rings. The NOB1 and NOB2 structures may be involved in these conformers, with the former of these two structures crystallizing as single crystals and with the latter soaking and being bound into the sponge.

As mentioned above, nobiletin has been reported to elicit a wide range of physiological responses. The key steps in these physiological responses are presumed to involve the binding of nobiletin to the target receptor molecules responsible for each physiological response. Nobiletin could bind to a wide range of receptors based on its conformational variety.

## Acknowledgements

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# supporting information

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## Nobiletin: a citrus flavonoid displaying potent physiological activity

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### Computing details

Data collection: *RAPID-AUTO* (Rigaku, 2010); cell refinement: *RAPID-AUTO* (Rigaku, 2010); data reduction: *RAPID-AUTO* (Rigaku, 2010); program(s) used to solve structure: *SHELXT* (Sheldrick, 2015*a*); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015*b*) and *shelXle* (Hübschle *et al.*, 2011); molecular graphics: *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2010).

### 2-(3,4-Dimethoxyphenyl)-5,6,7,8-tetramethoxy-4*H*-chromen-4-one

*Crystal data*

$C_{21}H_{22}O_8$
$M_r = 402.38$
Orthorhombic, $P2_12_12_1$
$a = 19.3239\ (17)$ Å
$b = 22.921\ (2)$ Å
$c = 4.1385\ (4)$ Å
$V = 1833.0\ (3)$ Å$^3$
$Z = 4$
$F(000) = 848$
$D_x = 1.458$ Mg m$^{-3}$
Synchrotron (SPring-8 BL02B1) radiation, $\lambda = 0.70041$ Å
Cell parameters from 377 reflections
$\theta = 2.8$–$29.5°$
$\mu = 0.11$ mm$^{-1}$
$T = 100$ K
Column, colourless
0.5 × 0.02 × 0.01 mm

*Data collection*

Rigaku Mercury2 CCD four-circle diffractometer
$\omega$ scan
13177 measured reflections
4894 independent reflections
4091 reflections with $I > 2\sigma(I)$
$R_{int} = 0.043$
$\theta_{max} = 29.6°$, $\theta_{min} = 1.4°$
$h = -26\rightarrow25$
$k = -32\rightarrow30$
$l = -5\rightarrow5$

*Refinement*

Refinement on $F^2$
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.065$
$wR(F^2) = 0.192$
$S = 1.29$
4894 reflections
268 parameters
0 restraints
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.42$ e Å$^{-3}$
$\Delta\rho_{min} = -0.29$ e Å$^{-3}$
Absolute structure: An arbitrary choice of enantiomer has been made.

*Special details*

**Geometry**. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

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

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| O2 | 0.86158 (13) | 0.29414 (11) | 0.2767 (8) | 0.0202 (6) |
| C2 | 0.70156 (19) | 0.36216 (16) | 0.4652 (10) | 0.0159 (7) |
| O1 | 0.66854 (13) | 0.32043 (11) | 0.6357 (7) | 0.0166 (6) |
| O3 | 0.85629 (13) | 0.18115 (11) | 0.5377 (7) | 0.0165 (6) |
| C3 | 0.76441 (19) | 0.35347 (16) | 0.3380 (11) | 0.0178 (8) |
| H3 | 0.7845 | 0.3837 | 0.2118 | 0.021* |
| O4 | 0.77681 (14) | 0.10365 (12) | 0.8750 (7) | 0.0196 (6) |
| C4 | 0.80334 (18) | 0.29972 (16) | 0.3846 (10) | 0.0157 (7) |
| C7 | 0.68406 (19) | 0.17222 (16) | 0.8978 (10) | 0.0160 (7) |
| O7 | 0.49217 (13) | 0.47574 (11) | 0.7082 (8) | 0.0213 (7) |
| O6 | 0.59535 (14) | 0.24399 (13) | 0.9566 (8) | 0.0218 (6) |
| C6 | 0.7513 (2) | 0.15775 (15) | 0.7931 (10) | 0.0164 (8) |
| O5 | 0.64380 (15) | 0.13367 (12) | 1.0635 (8) | 0.0247 (7) |
| C5 | 0.79098 (18) | 0.19812 (16) | 0.6319 (10) | 0.0154 (7) |
| C9 | 0.69935 (18) | 0.26729 (15) | 0.6807 (10) | 0.0147 (7) |
| O8 | 0.53896 (14) | 0.56400 (12) | 0.4006 (8) | 0.0220 (6) |
| C8 | 0.65893 (18) | 0.22752 (17) | 0.8452 (10) | 0.0161 (8) |
| C10 | 0.76586 (18) | 0.25431 (16) | 0.5686 (10) | 0.0143 (7) |
| C17 | 0.90960 (18) | 0.20222 (16) | 0.7489 (10) | 0.0172 (8) |
| H17A | 0.9536 | 0.1834 | 0.6937 | 0.021* |
| H17B | 0.8975 | 0.1930 | 0.9731 | 0.021* |
| H17C | 0.9141 | 0.2446 | 0.7240 | 0.021* |
| C11 | 0.66062 (19) | 0.41593 (16) | 0.4440 (10) | 0.0164 (7) |
| C18 | 0.7924 (2) | 0.06551 (17) | 0.6135 (12) | 0.0259 (9) |
| H18A | 0.7526 | 0.0634 | 0.4673 | 0.031* |
| H18B | 0.8027 | 0.0265 | 0.6977 | 0.031* |
| H18C | 0.8327 | 0.0804 | 0.4956 | 0.031* |
| C12 | 0.59492 (19) | 0.41848 (16) | 0.5923 (10) | 0.0169 (8) |
| H12 | 0.5775 | 0.3855 | 0.7054 | 0.020* |
| C19 | 0.6239 (2) | 0.08263 (18) | 0.8898 (14) | 0.0314 (11) |
| H19A | 0.6101 | 0.0935 | 0.6700 | 0.038* |
| H19B | 0.5849 | 0.0639 | 0.9999 | 0.038* |
| H19C | 0.6630 | 0.0555 | 0.8802 | 0.038* |
| C13 | 0.55586 (19) | 0.46892 (16) | 0.5732 (11) | 0.0176 (8) |
| C20 | 0.5402 (2) | 0.2274 (2) | 0.7441 (13) | 0.0325 (11) |
| H20A | 0.5338 | 0.1850 | 0.7530 | 0.039* |
| H20B | 0.5516 | 0.2390 | 0.5226 | 0.039* |
| H20C | 0.4973 | 0.2467 | 0.8115 | 0.039* |
| C14 | 0.58174 (19) | 0.51748 (16) | 0.4071 (11) | 0.0178 (8) |

| | | | | |
|---|---|---|---|---|
| C15 | 0.64615 (19) | 0.51500 (16) | 0.2609 (10) | 0.0179 (8) |
| H15 | 0.6635 | 0.5480 | 0.1478 | 0.021* |
| C16 | 0.68554 (19) | 0.46417 (16) | 0.2797 (11) | 0.0183 (8) |
| H16 | 0.7297 | 0.4626 | 0.1793 | 0.022* |
| C21 | 0.4644 (2) | 0.42762 (18) | 0.8763 (12) | 0.0229 (9) |
| H21A | 0.4580 | 0.3950 | 0.7263 | 0.027* |
| H21B | 0.4197 | 0.4385 | 0.9704 | 0.027* |
| H21C | 0.4963 | 0.4160 | 1.0488 | 0.027* |
| C22 | 0.5608 (2) | 0.61381 (17) | 0.2152 (12) | 0.0234 (9) |
| H22A | 0.5690 | 0.6020 | −0.0091 | 0.028* |
| H22B | 0.6036 | 0.6296 | 0.3072 | 0.028* |
| H22C | 0.5246 | 0.6438 | 0.2213 | 0.028* |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| O2 | 0.0153 (12) | 0.0178 (12) | 0.0276 (16) | 0.0012 (10) | 0.0076 (12) | 0.0015 (12) |
| C2 | 0.0165 (16) | 0.0169 (17) | 0.0142 (18) | −0.0031 (14) | −0.0036 (15) | −0.0003 (14) |
| O1 | 0.0135 (11) | 0.0127 (12) | 0.0235 (15) | 0.0001 (9) | 0.0000 (11) | 0.0013 (11) |
| O3 | 0.0160 (11) | 0.0156 (12) | 0.0181 (14) | 0.0003 (10) | −0.0015 (11) | −0.0037 (11) |
| C3 | 0.0184 (17) | 0.0144 (16) | 0.020 (2) | 0.0014 (14) | 0.0019 (15) | 0.0023 (16) |
| O4 | 0.0237 (13) | 0.0166 (12) | 0.0187 (15) | 0.0024 (10) | −0.0003 (12) | 0.0032 (11) |
| C4 | 0.0143 (15) | 0.0151 (16) | 0.0177 (19) | −0.0015 (13) | −0.0007 (15) | −0.0028 (15) |
| C7 | 0.0160 (15) | 0.0181 (17) | 0.0138 (18) | −0.0056 (13) | −0.0016 (15) | 0.0018 (15) |
| O7 | 0.0149 (12) | 0.0183 (13) | 0.0306 (18) | 0.0019 (10) | 0.0031 (12) | 0.0034 (13) |
| O6 | 0.0144 (12) | 0.0283 (15) | 0.0228 (16) | −0.0025 (11) | 0.0022 (12) | −0.0031 (13) |
| C6 | 0.0188 (16) | 0.0134 (16) | 0.0169 (19) | 0.0009 (13) | −0.0025 (15) | −0.0030 (15) |
| O5 | 0.0276 (14) | 0.0228 (14) | 0.0238 (17) | −0.0083 (12) | 0.0021 (13) | 0.0049 (13) |
| C5 | 0.0149 (15) | 0.0163 (16) | 0.0150 (18) | −0.0011 (13) | −0.0029 (15) | −0.0030 (15) |
| C9 | 0.0156 (16) | 0.0125 (16) | 0.0161 (18) | −0.0012 (13) | −0.0056 (14) | −0.0008 (14) |
| O8 | 0.0188 (12) | 0.0181 (13) | 0.0290 (17) | 0.0040 (10) | 0.0027 (12) | 0.0030 (13) |
| C8 | 0.0101 (14) | 0.0251 (19) | 0.0132 (18) | −0.0014 (13) | −0.0010 (14) | −0.0018 (15) |
| C10 | 0.0138 (15) | 0.0156 (16) | 0.0136 (18) | −0.0020 (13) | −0.0012 (14) | −0.0026 (14) |
| C17 | 0.0123 (15) | 0.0190 (17) | 0.020 (2) | 0.0041 (13) | −0.0013 (15) | 0.0005 (16) |
| C11 | 0.0147 (15) | 0.0156 (17) | 0.0188 (19) | −0.0003 (13) | −0.0019 (15) | −0.0031 (15) |
| C18 | 0.033 (2) | 0.0142 (17) | 0.030 (2) | 0.0000 (16) | 0.001 (2) | −0.0003 (17) |
| C12 | 0.0165 (16) | 0.0162 (17) | 0.018 (2) | −0.0010 (13) | −0.0003 (15) | 0.0001 (16) |
| C19 | 0.027 (2) | 0.0213 (19) | 0.046 (3) | −0.0099 (16) | 0.001 (2) | 0.002 (2) |
| C13 | 0.0131 (15) | 0.0188 (17) | 0.021 (2) | −0.0019 (13) | −0.0032 (15) | −0.0008 (16) |
| C20 | 0.0175 (19) | 0.056 (3) | 0.024 (2) | 0.0059 (19) | −0.0008 (18) | −0.002 (2) |
| C14 | 0.0195 (16) | 0.0157 (17) | 0.018 (2) | −0.0006 (13) | −0.0058 (16) | 0.0002 (16) |
| C15 | 0.0178 (16) | 0.0135 (16) | 0.022 (2) | −0.0006 (13) | 0.0010 (16) | 0.0003 (16) |
| C16 | 0.0127 (15) | 0.0189 (18) | 0.023 (2) | −0.0013 (13) | −0.0009 (15) | 0.0001 (16) |
| C21 | 0.0199 (17) | 0.025 (2) | 0.024 (2) | −0.0033 (15) | 0.0063 (17) | 0.0017 (18) |
| C22 | 0.0254 (19) | 0.0159 (17) | 0.029 (2) | 0.0043 (15) | −0.0011 (18) | 0.0020 (17) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| O2—C4 | 1.217 (4) | C17—H17B | 0.9800 |
| C2—C3 | 1.339 (5) | C17—H17C | 0.9800 |
| C2—O1 | 1.349 (4) | C11—C16 | 1.384 (5) |
| C2—C11 | 1.467 (5) | C11—C12 | 1.411 (5) |
| O1—C9 | 1.368 (4) | C18—H18A | 0.9800 |
| O3—C5 | 1.377 (4) | C18—H18B | 0.9800 |
| O3—C17 | 1.435 (5) | C18—H18C | 0.9800 |
| C3—C4 | 1.456 (5) | C12—C13 | 1.383 (5) |
| C3—H3 | 0.9500 | C12—H12 | 0.9500 |
| O4—C6 | 1.376 (4) | C19—H19A | 0.9800 |
| O4—C18 | 1.424 (5) | C19—H19B | 0.9800 |
| C4—C10 | 1.479 (5) | C19—H19C | 0.9800 |
| C7—O5 | 1.362 (5) | C13—C14 | 1.401 (5) |
| C7—C8 | 1.375 (5) | C20—H20A | 0.9800 |
| C7—C6 | 1.410 (5) | C20—H20B | 0.9800 |
| O7—C13 | 1.361 (4) | C20—H20C | 0.9800 |
| O7—C21 | 1.410 (5) | C14—C15 | 1.385 (5) |
| O6—C8 | 1.365 (4) | C15—C16 | 1.394 (5) |
| O6—C20 | 1.434 (5) | C15—H15 | 0.9500 |
| C6—C5 | 1.374 (5) | C16—H16 | 0.9500 |
| O5—C19 | 1.426 (5) | C21—H21A | 0.9800 |
| C5—C10 | 1.401 (5) | C21—H21B | 0.9800 |
| C9—C8 | 1.380 (5) | C21—H21C | 0.9800 |
| C9—C10 | 1.398 (5) | C22—H22A | 0.9800 |
| O8—C14 | 1.349 (4) | C22—H22B | 0.9800 |
| O8—C22 | 1.439 (5) | C22—H22C | 0.9800 |
| C17—H17A | 0.9800 | | |

| | | | |
|---|---|---|---|
| C3—C2—O1 | 122.0 (3) | O4—C18—H18B | 109.5 |
| C3—C2—C11 | 126.2 (4) | H18A—C18—H18B | 109.5 |
| O1—C2—C11 | 111.8 (3) | O4—C18—H18C | 109.5 |
| C2—O1—C9 | 119.8 (3) | H18A—C18—H18C | 109.5 |
| C5—O3—C17 | 113.0 (3) | H18B—C18—H18C | 109.5 |
| C2—C3—C4 | 122.8 (4) | C13—C12—C11 | 120.0 (3) |
| C2—C3—H3 | 118.6 | C13—C12—H12 | 120.0 |
| C4—C3—H3 | 118.6 | C11—C12—H12 | 120.0 |
| C6—O4—C18 | 116.2 (3) | O5—C19—H19A | 109.5 |
| O2—C4—C3 | 121.2 (3) | O5—C19—H19B | 109.5 |
| O2—C4—C10 | 124.6 (3) | H19A—C19—H19B | 109.5 |
| C3—C4—C10 | 114.2 (3) | O5—C19—H19C | 109.5 |
| O5—C7—C8 | 118.4 (3) | H19A—C19—H19C | 109.5 |
| O5—C7—C6 | 121.9 (3) | H19B—C19—H19C | 109.5 |
| C8—C7—C6 | 119.6 (3) | O7—C13—C12 | 124.5 (3) |
| C13—O7—C21 | 117.2 (3) | O7—C13—C14 | 115.7 (3) |
| C8—O6—C20 | 112.9 (3) | C12—C13—C14 | 119.8 (3) |
| C5—C6—O4 | 121.8 (3) | O6—C20—H20A | 109.5 |

| | | | |
|---|---|---|---|
| C5—C6—C7 | 120.3 (3) | O6—C20—H20B | 109.5 |
| O4—C6—C7 | 117.8 (3) | H20A—C20—H20B | 109.5 |
| C7—O5—C19 | 115.6 (3) | O6—C20—H20C | 109.5 |
| C6—C5—O3 | 117.3 (3) | H20A—C20—H20C | 109.5 |
| C6—C5—C10 | 121.1 (3) | H20B—C20—H20C | 109.5 |
| O3—C5—C10 | 121.6 (3) | O8—C14—C15 | 125.1 (4) |
| O1—C9—C8 | 114.1 (3) | O8—C14—C13 | 114.8 (3) |
| O1—C9—C10 | 123.0 (3) | C15—C14—C13 | 120.2 (3) |
| C8—C9—C10 | 122.9 (3) | C14—C15—C16 | 120.0 (4) |
| C14—O8—C22 | 117.3 (3) | C14—C15—H15 | 120.0 |
| O6—C8—C7 | 121.3 (3) | C16—C15—H15 | 120.0 |
| O6—C8—C9 | 119.6 (3) | C11—C16—C15 | 120.3 (3) |
| C7—C8—C9 | 119.2 (3) | C11—C16—H16 | 119.8 |
| C9—C10—C5 | 116.9 (3) | C15—C16—H16 | 119.8 |
| C9—C10—C4 | 118.1 (3) | O7—C21—H21A | 109.5 |
| C5—C10—C4 | 125.0 (3) | O7—C21—H21B | 109.5 |
| O3—C17—H17A | 109.5 | H21A—C21—H21B | 109.5 |
| O3—C17—H17B | 109.5 | O7—C21—H21C | 109.5 |
| H17A—C17—H17B | 109.5 | H21A—C21—H21C | 109.5 |
| O3—C17—H17C | 109.5 | H21B—C21—H21C | 109.5 |
| H17A—C17—H17C | 109.5 | O8—C22—H22A | 109.5 |
| H17B—C17—H17C | 109.5 | O8—C22—H22B | 109.5 |
| C16—C11—C12 | 119.6 (3) | H22A—C22—H22B | 109.5 |
| C16—C11—C2 | 120.8 (3) | O8—C22—H22C | 109.5 |
| C12—C11—C2 | 119.6 (3) | H22A—C22—H22C | 109.5 |
| O4—C18—H18A | 109.5 | H22B—C22—H22C | 109.5 |