Salvinorin B Methoxymethyl Ether

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Accessibility
Salvinorin B methoxymethyl ether

Thomas A. Munro, Douglas M. Ho and Bruce M. Cohen

The title compound [MOM-SalB; systematic name: methyl (2S,4aR,6aR,7R,9$\delta$10aS,10bR)-2-(3-furyl)-9-methoxymethoxy-6a,10b-dimethyl-4,10-dioxo-2,4a,5,6,7,8,9,10a-octahydro-1H-benzo[f]isochromene-7-carboxylate], C$_{23}$H$_{30}$O$_8$, is a derivative of the $\kappa$-opioid salvinorin A with enhanced potency, selectivity, and duration of action. Superimposition of their crystal structures reveals, surprisingly, that the terminal C and O atoms of the MOM group overlap with the corresponding atoms in salvinorin A, which are separated by an additional bond. This counter-intuitive isosterism is possible because the MOM ether adopts the ‘classic anomeric’ conformation (gauche–gauche), tracing a helix around the planar acetate of salvinorin A. This overlap is not seen in the recently reported structure of the tetrahydropyranyl ether, which is less potent. The classic anomeric conformation is strongly favoured in alkoxymethyl ethers, but not in substituted acetics, which may contribute to their reduced potency. This structure may prove useful in evaluating models of the activated $\kappa$-opioid receptor.

Related literature

For preparation, see: Béguin et al. (2009). For amended characterization data, see: Munro et al. (2008). For structure–activity relationships in vitro, see: Béguin et al. (2012); Munro et al. (2008); Prevatt-Smith et al. (2011). For in vivo pharmacology, see: Baker et al. (2009); Peet & Baker (2011); Wang et al. (2008). For pharmacokinetics and PET imaging of the ethoxymethyl ether, see: Hooker et al. (2009). For structure–activity relationships of salvinorin A, see: Cunningham et al. (2011). For crystal structures of related compounds, see: Ortega et al. (1982); Prevatt-Smith et al. (2011); Tidgewell et al. (2006). For solid-state and bioactive conformations of acetics, see: Anderson (2000); Brameld et al. (2008).

References

Anderson, J. E. (2000). J. Org. Chem., 65, 748–754.
Baker, L. E., Panos, J. J., Killinger, B. A., Peet, M. M., Bell, L. M., Haliw, L. A. & Walker, S. L. (2009). Psychopharmacology (Berlin), 203, 203–211.
Béguin, C., Carlezon, W. A. Jr, Cohen, B. M., He, M., Lee, D. Y.-W., Richards, M. R. & Liu-Chen, L.-Y. (2009). US Patent No. 7,629,475.
Béguin, C., Potuzak, J., Xu, W., Liu-Chen, L.-Y., Streicher, J. M., Groer, C. E., Bohn, L. M., Carlezon, W. A. Jr & Cohen, B. M. (2012). Bioorg. Med. Chem. Lett. 22, 1023–1026.
Brameld, K. A., Kuhn, B., Reuter, D. C. & Stahl, M. (2008). J. Chem. Inf. Model. 48, 1–24.
Brameld, K. A., Kuhn, B., Reuter, D. C. & Stahl, M. (2008). J. Chem. Inf. Model. 48, 1–24.
Bruker (2004). SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2006). APEX2 and SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: QM2086).

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organic compounds

Cunningham, C. W., Rothman, R. B. & Prisinzano, T. E. (2011). *Pharmacol. Rev.* **63**, 316–347.

DeLano, W. L. (2009). *pyMOL*. DeLano Scientific LLC, San Carlos, California, USA.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Hooker, J. M., Munro, T. A., Béguin, C., Alexoff, D., Shea, C., Xu, Y. & Cohen, B. M. (2009). *Neuropharmacology* **57**, 386–391.

Munro, T. A., Duncan, K. K., Xu, W., Wang, Y., Liu-Chen, L.-Y., Carlezon, W. A. Jr, Cohen, B. M. & Béguin, C. (2008). *Bioorg. Med. Chem.* **16**, 1279–1286.

Ortega, A., Blount, J. F. & Manchand, P. S. (1982). *J. Chem. Soc. Perkin Trans. 1*, pp. 2505–2508.

Peet, M. M. & Baker, L. E. (2011). *Behav. Pharmacol.* **22**, 450–457.

Prevatt-Smith, K. M., Lovell, K. M., Simpson, D. S., Day, V. W., Douglas, J. T., Bosch, P., Dersch, C. M., Rothman, R. B., Kivell, B. & Prisinzano, T. E. (2011). *MedChemComm* **2**, 1217–1222.

Sheldrick, G. M. (2008). *Acta Cryst. A* **64**, 112–122.

Tidgewell, K., Harding, W. W., Lozama, A., Cobb, H., Shah, K., Kannan, P., Dersch, C. M., Parrish, D., Deschamps, J. R., Rothman, R. B. & Prisinzano, T. E. (2006). *J. Nat. Prod.* **69**, 914–918.

Wang, Y., Chen, Y., Xu, W., Lee, D. Y., Ma, Z., Rawls, S. M., Cowan, A. & Liu-Chen, L. Y. (2008). *J. Pharmacol. Exp. Ther.* **324**, 1073–1083.
Salvinorin B methoxymethyl ether

Thomas A. Munro, Douglas M. Ho and Bruce M. Cohen

Comment

Salvinorin B methoxymethyl ether (1) is among the most potent and selective \(\kappa\) (kappa) opioids known, with subnanomolar affinity and potency (Wang et al., 2008). A semisynthetic derivative of the naturally occurring \(\kappa\) opioid salvinorin A (2), (1) was the first derivative reported to be more potent than (2) \textit{in vitro}, and also showed greater potency and duration of action in mice (Wang et al., 2008). The extreme potency of (1) has been confirmed both \textit{in vitro} (Munro et al., 2008, Prevatt-Smith et al., 2011) and \textit{in vivo} (Baker et al., 2009, Peet & Baker, 2011). The name MOM-SalB is widely used; the incorrect name ‘2-methoxymethylsalvinorin B’, implying that the substituent is directly attached to C2, should be avoided.

In Figure 1, the structures of (1) and (2) have been drawn to emphasize their similarity, with O2, C21 and O3 superimposable. The terminal methyl group C22 is attached to O3 in (1) but C21 in (2), and might be expected to interact with different regions of the receptor. Extensive research has been done into the structure-activity relationships of (2), especially the role of the C2 acetate. The deacetyl analogue salvinorin B is at least 60-fold less potent than (2). Deoxygenation or demethylation of the acetate causes smaller reductions in potency (Cunningham et al., 2011). This suggests that the two extremities of the acetate (O3 and C22) engage in separate, synergistic interactions with the binding pocket (Munro et al., 2008). The structure-activity relationships of (1) have also been explored. Potency is dramatically reduced by replacement of O3 with sulfur or carbon (Munro et al., 2008); this similarity to (2) is consistent with the proposed common binding pose. The ethoxymethyl ether (3) appears to be even more potent and selective than (1), both \textit{in vitro} (Munro et al., 2008, Prevatt-Smith et al., 2011) and \textit{in vivo} (Baker et al., 2009, Peet & Baker, 2011). Similarly, 12-epi-(3) reportedly exhibits higher affinity than 12-epi-(1) (Béguin et al., 2012). Further extension or branching of the terminal alkyl chain reduces affinity (Munro et al., 2008). Thus, the ethoxymethyl substituent appears to confer optimal affinity and potency. Like (1), (3) is also metabolized more slowly than (2) (Hooker et al., 2009). Based on the above hypothesis that the C22 methyl groups in (1) and (2) address different regions of the binding pocket, ethoxyethyl ether (4) was designed in that hope that it would interact with both of these regions, maximizing affinity. However, upon testing, (4) proved to have much lower affinity and potency than (3) (Munro et al., 2008, Prevatt-Smith et al., 2011). Indeed, all derivatives tested to date featuring substituted acetals, such as (5), exhibit reduced affinity and potency (Munro et al., 2008, Prevatt-Smith et al., 2011). These surprising and disappointing results cast doubt on the proposed binding model.

We therefore determined the structure of (1) by single-crystal X-ray diffraction to obtain conformational information (Figure 2).

Other than the disordered furan ring, the neoclerodane scaffold is almost perfectly superimposable (r.m.s. < 0.1 Å) upon that of (2), as expected (Ortega et al., 1982). However, the resulting relationship between the acetate and the MOM ether was unexpected. Both O3 and C22 in (1) overlap with their counterparts in (2), being separated by just 0.9 Å (O3) and 1.2 Å (C22) – less than their atomic radii. The overlapping van der Waals surfaces of O3 and C22 are shown in Figure 3. This result was surprising, given the different point of attachment of C22 in these two compounds (Figure 1). This
counterintuitive result occurs because both bonds to the acetal carbon C21 in (1) are gauche (torsion angles: 69.8° (O2—C22) and 76.5° (C2—O3)), allowing the ether to trace a part helix around the planar acetate in (2). This is known as the ‘classic anomeric’ conformation (Anderson, 2000, Brameld et al., 2008). Generally, solid-state conformations coincide closely with the bioactive conformation of the protein-bound ligand (Brameld et al., 2008). This is because both solid-state and bound conformations tend toward the free energy minimum. The similarity is greatest in high-affinity ligands, since any change in conformation during binding requires energy, and this ‘energetic penalty’ reduces affinity (Brameld et al., 2008). As discussed above, structure-activity studies indicate that O3 and C22 contribute substantially to binding of both (2) and (1). The near-superimposability of these atoms in the crystal structures of these two high-affinity ligands suggests that they may represent similar bioactive conformations. Alkoxyalkyl ethers invariably adopt the classic anomic conformation, due to strong anomic interactions involving both O atoms (Anderson, 2000, Brameld et al., 2008). Interestingly, however, substitution of the acetal carbon introduces steric interactions which greatly reduce this preference. With a methyl substituent, as in (4), the classic anomic conformation predominates, but is not exclusive. With larger substituents this conformation is strongly disfavoured, and rarely occurs (Anderson, 2000). If the classic anomic conformation seen in (1) is optimal for binding, acetal substitution would therefore be expected to reduce affinity by this conformational influence, even if the substituents do not themselves interact unfavourably with the receptor. This may contribute to the dramatic reductions in affinity and potency seen even with small acetal substituents (Munro et al., 2008, Prevatt-Smith et al., 2011).

The recently reported crystal structure of the tetrahydropyranyl (THP) ether (5) illustrates this point (Prevatt-Smith et al., 2011). The cyclic acetal does not adopt the classic anomic conformation, and superimposition on (2) gives much poorer overlap than seen with (1) (Figure 4). Acetal oxygen O3 is separated from its counterpart in (2) by 2.5 Å, and is instead almost coincident with C22 (<0.2 Å). Furthermore, the THP ring is disordered, consisting of a mixture of two interconvertible chair conformations. Thus, the THP ether exhibits weaker conformational preferences than the MOM ether, and much poorer overlap with (2). This may partly account for its lower potency. Our results suggest a possible conformational basis for the high binding affinity of salvinorin B alkoxyethyl ethers such as (1) and (3), and for the reduced affinity of substituted acetal derivatives such as (4) and (5). As a structurally atypical and extremely potent agonist, the structure of (1) reported here may prove useful in modelling the activation of the κ opioid receptor.

Experimental

Compound (1) was prepared as described previously, by treatment of salvinorin B with CH3OCH2Cl and i-Pr2NEt in anhydrous CH2Cl2, and purified by flash chromatography on silica gel (Béguin et al., 2009). Amended characterization data have been reported elsewhere (Munro et al., 2008). Dissolution of 200 mg in minimal boiling methanol (~3 ml) and slow cooling gave colourless needles, mp 165–167 °C (438–440 K).

Refinement

The 3-furyl substituent was treated with a two-site disorder model consisting of [O8, C13, C14, C15, C16] and [O8*, C13*, C14*, C15*, C16*] with refined site occupancy factors of 0.66 (2) and 0.34 (2), respectively. These ten atoms were included in the least-squares refinement with rigid bond, similar $U_{ij}$, common plane and 1,2-distance restraints. All H atoms were allowed to ride on their respective C atoms with C—H distances constrained to the SHELXTL (Sheldrick, 2008) default values for the specified functional groups at 193 K, i.e., 0.95, 0.98, 0.99 and 1.00 Å for the olefinic, methyl, methylene and methine H atoms, respectively. The $U_{eq}(H)$ values were set at 1.5 $U_{eq}(C)$ for the methyl H atoms and 1.2 $U_{eq}(C)$ for all others. The Flack parameter obtained [$x = 0.2 (7)$] was inconclusive. The absolute stereochemistry of salvinorin B has been established via the $p$-bromobenzoate (Tidgewell et al., 2006).
Computing details

Data collection: APEX2 (Bruker, 2006); cell refinement: SAINT (Bruker, 2006); data reduction: SAINT (Bruker, 2006); program(s) used to solve structure: SHELXTL (Sheldrick, 2008); program(s) used to refine structure: SHELXTL (Sheldrick, 2008); molecular graphics: ORTEP-3 (Farrugia, 1997) and pyMOL (DeLano, 2009); software used to prepare material for publication: SHELXTL (Sheldrick, 2008).

Figure 1

Structures of compounds discussed.

Figure 2

Crystal structure of (1) with 50% probability thermal displacement ellipsoids. Atom numbering follows the crystal structure of (2) (Ortega et al., 1982) (* = minor component of disorder) (Cross-eyed stereoview).
Figure 3
Superimposed structures of (1) in blue and (2) in black (CSD code BUJJIZ, Ortega et al., 1982). Spheres represent the van der Waals surfaces of O3 and C22, connected by dotted yellow lines (Cross-eyed stereoview).
Figure 4
Superimposed structures of (2) in black with (5) in blue (major component) and purple (minor component) (CCDC 837303, Prevatt-Smith et al., 2011). Spheres represent the van der Waals surface of O3, connected by dotted yellow lines (Cross-eyed stereoview).

Methyl (2S,4aR,6aR,7R,9S,10aS,10bR)-2-(3-furyl)-9-methoxymethoxy-6a,10b-dimethyl-4,10-dioxo-2,4a,5,6,7,8,9,10a-octahydro-1H-benzo[f]isochromene-7-carboxylate

Crystal data
\[ \text{C}_{23}\text{H}_{30}\text{O}_8 \]  
\[ M_r = 434.47 \]  
Monoclinic, C2  
Hall symbol: C 2y  
\[ a = 27.8848 \text{ (7) Å} \]  
\[ b = 6.2415 \text{ (2) Å} \]  
\[ c = 12.8212 \text{ (3) Å} \]  
\[ \beta = 107.351 \text{ (1)°} \]  
\[ V = 2129.9 \text{ (1) Å}^3 \]  
\[ Z = 4 \]  
\[ F(000) = 928 \]  
\[ D_x = 1.355 \text{ Mg m}^{-3} \]
Melting point = 438–440 K  
Mo Kα radiation, λ = 0.71073 Å  
Cell parameters from 9071 reflections  
θ = 3.0–29.5°  
µ = 0.10 mm⁻¹  
T = 193 K  
Needle, colourless  
0.25 × 0.13 × 0.07 mm

Data collection

Bruker APEXII CCD  
diffractometer  
Radiation source: fine-focus sealed tube  
Graphite monochromator  
Detector resolution: 836.6 pixels mm⁻¹  
ω scans, 2580 0.5° rotations  
Absorption correction: multi-scan  
(SADABS; Bruker, 2004)  
Tmin = 0.975, Tmax = 0.993

Refinement

Refinement on F²  
Least-squares matrix: full  
R[F² > 2σ(F²)] = 0.040  
wR(F²) = 0.108  
S = 1.04  
6195 reflections  
330 parameters  
181 restraints  
Primary atom site location: structure-invariant direct methods  
Secondary atom site location: difference Fourier map  
Hydrogen site location: inferred from neighbouring sites  
H-atom parameters constrained  
Δρmax = 0.28 e Å⁻³  
Δρmin = −0.16 e Å⁻³

Special details

Refinement. Refinement of F² against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F², conventional R-factors R are based on F, with F set to zero for negative F². The threshold expression of F² > 2σ(F²) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F² are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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

|   | x    | y    | z    | Uiso/*Ueq | Occ. (<1) |
|---|------|------|------|-----------|-----------|
| O1| 0.34600 (4) | 1.0459 (2) | 0.20598 (9) | 0.0363 (3) |
| O2| 0.37399 (4) | 1.1271 (2) | 0.02768 (10) | 0.0382 (3) |
| O3| 0.28986 (5) | 1.1470 (3) | −0.07126 (12) | 0.0533 (3) |
| O4| 0.50180 (4) | 0.3453 (2) | 0.13791 (9) | 0.0347 (2) |
| O5| 0.53410 (4) | 0.6752 (2) | 0.15051 (11) | 0.0434 (3) |
| O6| 0.31648 (4) | 0.4502 (3) | 0.48120 (9) | 0.0436 (3) |
| O7| 0.39036 (5) | 0.3347 (3) | 0.57679 (9) | 0.0458 (3) |
| O8| 0.1529 (2) | 0.3841 (16) | 0.3150 (5) | 0.0598 (16) | 0.66 (2) |
| O8*| 0.1624 (5) | 0.306 (3) | 0.3130 (11) | 0.065 (3) | 0.34 (2) |
| C1| 0.36787 (5) | 0.9006 (2) | 0.17700 (11) | 0.0249 (3) |
| C2| 0.38017 (5) | 0.9135 (3) | 0.06823 (11) | 0.0283 (3) |
| H2| 0.3558 | 0.8201 | 0.0142 | 0.034* |
| C3| 0.43320 (5) | 0.8377 (3) | 0.07636 (12) | 0.0315 (3) |
| H3A| 0.4360 | 0.8163 | 0.0019 | 0.038* |
| H3B| 0.4576 | 0.9499 | 0.1126 | 0.038* |
| C4| 0.44644 (5) | 0.6293 (3) | 0.14044 (11) | 0.0257 (3) |
### supplementary materials

| Atom | X     | Y     | Z     | Temperature Anisotropy Coefficients |
|------|-------|-------|-------|-------------------------------------|
| H4   | 0.422 | 0.517 | 0.100 | 0.031*                              |
| C5   | 0.441 | 0.650 | 0.258 | 0.022 (2)                           |
| C6   | 0.455 | 0.436 | 0.318 | 0.026 (3)                           |
| H6A  | 0.439 | 0.318 | 0.269 | 0.032*                              |
| H6B  | 0.492 | 0.417 | 0.338 | 0.032*                              |
| C7   | 0.439 | 0.422 | 0.422 | 0.027 (3)                           |
| H7A  | 0.449 | 0.281 | 0.457 | 0.033*                              |
| H7B  | 0.456 | 0.536 | 0.473 | 0.033*                              |
| C8   | 0.383 | 0.447 | 0.394 | 0.024 (3)                           |
| H8   | 0.368 | 0.334 | 0.339 | 0.029*                              |
| C9   | 0.363 | 0.664 | 0.340 | 0.023 (2)                           |
| C10  | 0.383 | 0.692 | 0.239 | 0.022 (2)                           |
| H10  | 0.365 | 0.578 | 0.188 | 0.027*                              |
| C11  | 0.306 | 0.635 | 0.300 | 0.029 (3)                           |
| H11A | 0.290 | 0.769 | 0.264 | 0.035*                              |
| H11B | 0.298 | 0.519 | 0.244 | 0.035*                              |
| C12  | 0.283 | 0.578 | 0.392 | 0.032 (3)                           |
| H12  | 0.277 | 0.716 | 0.424 | 0.038*                              |
| H12* | 0.274 | 0.713 | 0.423 | 0.038*                              |
| C13  | 0.234 | 0.460 | 0.352 | 0.039 (4)                           |
| C14  | 0.224 | 0.254 | 0.303 | 0.060 (6)                           |
| H14  | 0.248 | 0.163 | 0.286 | 0.073*                              |
| C15  | 0.176 | 0.212 | 0.282 | 0.057 (5)                           |
| H15  | 0.160 | 0.083 | 0.255 | 0.069*                              |
| C16  | 0.189 | 0.534 | 0.357 | 0.050 (7)                           |
| H16  | 0.184 | 0.694 | 0.385 | 0.061*                              |
| C13* | 0.237 | 0.442 | 0.351 | 0.032 (4)                           |
| C14* | 0.235 | 0.241 | 0.298 | 0.044 (4)                           |
| H14* | 0.263 | 0.172 | 0.285 | 0.052*                              |
| C15* | 0.189 | 0.165 | 0.268 | 0.062 (5)                           |
| H15* | 0.176 | 0.041 | 0.226 | 0.075*                              |
| C16* | 0.191 | 0.481 | 0.359 | 0.042 (5)                           |
| H16* | 0.180 | 0.604 | 0.389 | 0.051*                              |
| C17  | 0.364 | 0.408 | 0.491 | 0.032 (4)                           |
| C18  | 0.499 | 0.558 | 0.143 | 0.029 (3)                           |
| C19  | 0.474 | 0.830 | 0.320 | 0.029 (3)                           |
| H19A | 0.508 | 0.813 | 0.314 | 0.044*                              |
| H19B | 0.476 | 0.822 | 0.398 | 0.044*                              |
| H19C | 0.462 | 0.969 | 0.290 | 0.044*                              |
| C20  | 0.378 | 0.847 | 0.426 | 0.031 (3)                           |
| H20A | 0.366 | 0.812 | 0.488 | 0.047*                              |
| H20B | 0.363 | 0.981 | 0.392 | 0.047*                              |
| H20C | 0.414 | 0.862 | 0.450 | 0.047*                              |
| C21  | 0.338 | 1.153 | −0.075 | 0.048 (5)                           |
| H21A | 0.345 | 1.292 | −0.106 | 0.058*                              |
| H21B | 0.343 | 1.039 | −0.124 | 0.058*                              |
| C22  | 0.277 | 1.329 | −0.019 | 0.065 (6)                           |
| H22A | 0.240 | 1.333 | −0.033 | 0.098*                              |
| H22B | 0.287 | 1.459 | −0.048 | 0.098*                              |

* Supercell factors are given in parentheses.
## Atomic displacement parameters (Å²)

|   | $U^{11}$   | $U^{22}$   | $U^{33}$   | $U^{12}$   | $U^{13}$   | $U^{23}$   |
|---|------------|------------|------------|------------|------------|------------|
| O1| 0.0463 (6) | 0.0288 (5) | 0.0338 (6) | 0.0112 (5) | 0.0120 (5) | 0.0024 (4) |
| O2| 0.0313 (5) | 0.0392 (6) | 0.0420 (6) | 0.0014 (5) | 0.0073 (4) | 0.0178 (5) |
| O3| 0.0365 (6) | 0.0615 (9) | 0.0539 (8) | 0.0058 (6) | 0.0015 (5) | −0.0023 (7) |
| O4| 0.0311 (5) | 0.0329 (5) | 0.0440 (6) | 0.0031 (4) | 0.0170 (5) | −0.0081 (5) |
| O5| 0.0319 (5) | 0.0406 (7) | 0.0629 (8) | −0.0012 (5) | 0.0221 (5) | 0.0062 (6) |
| O6| 0.0355 (6) | 0.0683 (8) | 0.0309 (6) | 0.0052 (6) | 0.0160 (5) | 0.0144 (6) |
| O7| 0.0433 (6) | 0.0649 (8) | 0.0291 (6) | 0.0023 (6) | 0.0105 (5) | 0.0140 (6) |
| O8| 0.0397 (17)| 0.096 (4)  | 0.0512 (16)| −0.019 (2) | 0.0254 (14)| −0.016 (2) |
| O8*| 0.047 (4) | 0.086 (7)  | 0.072 (5)  | −0.019 (4) | 0.032 (3)  | 0.007 (4)  |
| C1| 0.0239 (6) | 0.0249 (6) | 0.0237 (6) | −0.0013 (5) | 0.0039 (5) | −0.0001 (5) |
| C2| 0.0283 (6) | 0.0299 (7) | 0.0266 (6) | −0.0006 (6) | 0.0081 (5) | 0.0056 (6) |
| C3| 0.0312 (7) | 0.0364 (7) | 0.0297 (7) | 0.0035 (6) | 0.0135 (6) | 0.0075 (6) |
| C4| 0.0252 (6) | 0.0288 (7) | 0.0250 (6) | −0.0006 (5) | 0.0103 (5) | 0.0000 (5) |
| C5| 0.0239 (6) | 0.0211 (6) | 0.0239 (6) | −0.0001 (5) | 0.0077 (5) | 0.0000 (5) |
| C6| 0.0291 (7) | 0.0223 (6) | 0.0301 (7) | 0.0026 (5) | 0.0109 (5) | 0.0021 (5) |
| C7| 0.0289 (6) | 0.0265 (6) | 0.0269 (6) | 0.0026 (5) | 0.0082 (5) | 0.0051 (5) |
| C8| 0.0284 (6) | 0.0227 (6) | 0.0228 (6) | −0.0021 (5) | 0.0086 (5) | −0.0002 (5) |
| C9| 0.0257 (6) | 0.0239 (6) | 0.0227 (6) | 0.0010 (5) | 0.0094 (5) | −0.0004 (5) |
| C10| 0.0247 (6)| 0.0215 (6)| 0.0213 (6)| −0.0004 (5)| 0.0078 (5)| −0.0006 (5)|
| C11| 0.0267 (6)| 0.0371 (7)| 0.0254 (7)| 0.0017 (6)| 0.0107 (5)| 0.0028 (6)|
| C12| 0.0308 (7)| 0.0376 (8)| 0.0306 (7)| 0.0020 (6)| 0.0137 (6)| 0.0021 (6)|
| C13| 0.045 (3)| 0.040 (2)| 0.037 (3)| −0.006 (2)| 0.015 (3)| 0.007 (2)|
| C14| 0.060 (3)| 0.046 (2)| 0.083 (3)| 0.001 (3)| 0.033 (3)| 0.001 (2)|
| C15| 0.064 (4)| 0.057 (3)| 0.063 (2)| −0.024 (3)| 0.035 (2)| −0.015 (2)|
| C16| 0.043 (2)| 0.071 (4)| 0.042 (3)| −0.007 (2)| 0.0173 (18)| −0.008 (3)|
| C13*| 0.022 (3)| 0.043 (5)| 0.037 (5)| 0.005 (3)| 0.018 (3)| 0.003 (4)|
| C14*| 0.035 (3)| 0.031 (3)| 0.070 (4)| −0.011 (3)| 0.024 (3)| −0.017 (3)|
| C15*| 0.046 (5)| 0.049 (4)| 0.098 (6)| −0.022 (4)| 0.031 (4)| −0.010 (4)|
| C16*| 0.034 (4)| 0.067 (5)| 0.038 (4)| 0.007 (3)| 0.030 (3)| 0.012 (4)|
| C17| 0.0345 (7)| 0.0362 (8)| 0.0271 (7)| −0.0030 (6)| 0.0114 (6)| 0.0015 (6)|
| C18| 0.0281 (7)| 0.0346 (7)| 0.0285 (7)| 0.0012 (6)| 0.0126 (6)| 0.0014 (6)|
| C19| 0.0300 (7)| 0.0259 (6)| 0.0309 (7)| −0.0046 (6)| 0.0073 (5)| −0.0023 (6)|
| C20| 0.0402 (8)| 0.0281 (7)| 0.0273 (7)| −0.0001 (6)| 0.0121 (6)| −0.0041 (6)|
| C21| 0.0445 (9)| 0.0660 (12)| 0.0357 (9)| 0.0152 (9)| 0.0126 (7)| 0.0210 (9)|
| C22| 0.0532 (12)| 0.0669 (14)| 0.0752 (15)| 0.0227 (11)| 0.0176 (11)| 0.0014 (13)|
| C23| 0.0338 (8)| 0.0450 (9)| 0.0468 (10)| 0.0088 (7)| 0.0172 (7)| −0.0058 (7)|

## Geometric parameters (Å, °)

|   | O1—C1  | 1.2112 (17) | C9—C11 | 1.5404 (19) |
|---|--------|-------------|--------|-------------|
| O2—C21 | 1.400 (2) | C9—C20 | 1.543 (2) |
O2—C2 1.4225 (18) C9—C10 1.5586 (17)
O3—C21 1.373 (2) C10—H10 1.0000
O3—C22 1.420 (3) C11—C12 1.5340 (19)
O4—C18 1.3305 (19) C11—H11A 0.9900
O4—C23 1.4513 (18) C11—H11B 0.9900
O5—C18 1.2067 (19) C12—C13* 1.500 (3)
O6—C17 1.3404 (18) C12—C13 1.501 (2)
O6—C12 1.4715 (19) C12—H12 1.0000
O7—C17 1.2040 (19) C12—H12* 1.0000
O8—C16 1.377 (3) C13—C16 1.346 (3)
O8—C15 1.385 (3) C13—C14 1.423 (3)
O8*—C16* 1.378 (3) C14—C15 1.320 (3)
O8*—C15* 1.380 (3) C14—H14 0.9500
C1—C10 1.5214 (18) C15—H15 0.9500
C1—C2 1.5344 (18) C16—H16 0.9500
C2—C3 1.5263 (19) C13*—C16* 1.349 (3)
C2—H2 1.0000 C13*—C14* 1.423 (3)
C3—C4 1.524 (2) C14*—C15* 1.320 (3)
C3—H3A 0.9900 C14*—H14* 0.9500
C3—H3B 0.9900 C15*—H15* 0.9500
C4—C18 1.5198 (19) C16*—H16* 0.9500
C4—C5 1.5617 (18) C19—H19A 0.9800
C4—H4 1.0000 C19—H19B 0.9800
C5—C19 1.5340 (19) C19—H19C 0.9800
C5—C6 1.5390 (19) C20—H20A 0.9800
C5—C10 1.5778 (17) C20—H20B 0.9800
C6—C7 1.5216 (19) C20—H20C 0.9800
C6—H6A 0.9900 C21—H21A 0.9900
C6—H6B 0.9900 C21—H21B 0.9900
C7—C8 1.5147 (19) C22—H22A 0.9800
C7—H7A 0.9900 C22—H22B 0.9800
C7—H7B 0.9900 C22—H22C 0.9800
C8—C17 1.5054 (18) C23—H23A 0.9800
C8—C9 1.5415 (19) C23—H23B 0.9800
C8—H8 1.0000 C23—H23C 0.9800

C21—O2—C2 115.33 (14) O6—C12—C13 106.9 (5)
C21—O3—C22 112.85 (17) O6—C12—C11 114.68 (11)
C18—O4—C23 116.56 (13) C13*—C12—C11 111.9 (9)
C17—O6—C12 123.97 (11) C13—C12—C11 113.2 (5)
C16—O8—C15 106.2 (4) O6—C12—H12 107.2
C16*—O8*—C15* 111.6 (8) C13—C12—H12 107.2
O1—C1—C10 124.47 (12) C11—C12—H12 107.2
O1—C1—C2 120.59 (12) O6—C12—H12* 108.8
C10—C1—C2 114.89 (11) C13*—C12—H12* 108.8
O2—C2—C3 108.95 (11) C11—C12—H12* 108.8
O2—C2—H2 110.23 (12) C16—C13—C14 105.5 (4)
C3—C2—C1 113.35 (11) C16—C13—C12 125.2 (5)
C3—C2—H2 108.1 C14—C13—C12 129.3 (6)
| Bond/Geometry | Value 1 | Bond/Geometry | Value 2 | Value 3 |
|---------------|---------|---------------|---------|---------|
| C3—C2—H2     | 108.1   | C15—C14—C13  | 108.8   |
| C1—C2—H2     | 108.1   | C15—C14—H14  | 125.6   |
| C4—C3—C2     | 112.05  | C13—C14—H14  | 125.6   |
| C4—C3—H3A    | 109.2   | C14—C15—O8   | 109.2   |
| C2—C3—H3A    | 109.2   | C14—C15—H15  | 125.4   |
| C4—C3—H3B    | 109.2   | O8—C15—H15   | 125.4   |
| C2—C3—H3B    | 109.2   | C13—C16—O8   | 110.3   |
| H3A—C3—H3B   | 107.9   | C13—C16—H16  | 124.8   |
| C18—C4—C3    | 109.94  | O8—C16—H16   | 124.8   |
| C18—C4—C5    | 111.73  | C16*—C13*—C14* | 107.1  |
| C3—C4—C5     | 111.70  | C16*—C13*—C12 | 128.0  |
| C18—C4—H4    | 107.8   | C14*—C13*—C12 | 124.9  |
| C3—C4—H4     | 107.8   | C15*—C14*—C13* | 110.3  |
| C5—C4—H4     | 107.8   | C15*—C14*—H14* | 124.8  |
| C19—C5—C6    | 109.92  | C13*—C14*—H14* | 124.8  |
| C19—C5—C4    | 110.34  | C14*—C15*—O8* | 104.9  |
| C6—C5—C4     | 109.16  | C14*—C15*—H15* | 127.6  |
| C19—C5—C10   | 113.43  | O8*—C15*—H15* | 127.6  |
| C6—C5—C10    | 108.71  | C13*—C16*—O8* | 105.6  |
| C4—C5—C10    | 105.12  | C13*—C16*—H16* | 127.2  |
| C7—C6—C5     | 113.11  | O8*—C16*—H16* | 127.2  |
| C7—C6—H6A    | 109.0   | O7—C17—O6    | 117.96  |
| C5—C6—H6A    | 109.0   | O7—C17—C8    | 124.09  |
| C7—C6—H6B    | 109.0   | O6—C17—C8    | 117.89  |
| C5—C6—H6B    | 109.0   | O5—C18—O4    | 123.31  |
| H6A—C6—H6B   | 109.0   | O5—C18—C4    | 125.31  |
| C8—C7—C6     | 109.78  | O4—C18—C4    | 111.38  |
| C8—C7—H7A    | 109.7   | C5—C19—H19A  | 109.5   |
| C6—C7—H7A    | 109.7   | C5—C19—H19B  | 109.5   |
| C8—C7—H7B    | 109.7   | H19A—C19—H19B | 109.5  |
| C6—C7—H7B    | 109.7   | C5—C19—H19C  | 109.5   |
| H7A—C7—H7B   | 108.2   | H19A—C19—H19C | 109.5  |
| C17—C8—C7    | 111.86  | H19B—C19—H19C | 109.5  |
| C17—C8—C9    | 110.35  | C9—C20—H20A  | 109.5   |
| C7—C8—C9     | 113.75  | C9—C20—H20B  | 109.5   |
| C17—C8—H8    | 106.8   | H20A—C20—H20B | 109.5  |
| C7—C8—H8     | 106.8   | C9—C20—H20C  | 109.5   |
| C9—C8—H8     | 106.8   | H20A—C20—H20C | 109.5  |
| C11—C9—C8    | 103.83  | H20B—C20—H20C | 109.5  |
| C11—C9—C20   | 110.78  | O3—C21—O2    | 113.10  |
| C8—C9—C20    | 110.59  | O3—C21—H21A  | 109.0   |
| C11—C9—C10   | 108.70  | O2—C21—H21A  | 109.0   |
| C8—C9—C10    | 107.52  | O3—C21—H21B  | 109.0   |
| C20—C9—C10   | 114.80  | O2—C21—H21B  | 109.0   |
| C1—C10—C9    | 114.89  | H21A—C21—H21B | 107.8  |
| C1—C10—C5    | 109.55  | O3—C22—H22A  | 109.5   |
| C9—C10—C5    | 117.10  | O3—C22—H22B  | 109.5   |
| C1—C10—H10   | 104.6   | H22A—C22—H22B | 109.5  |
| C9—C10—H10   | 104.6   | O3—C22—H22C  | 109.5   |
supplementary materials

C5—C10—H10 104.6
C12—C11—C9 113.17 (11)
C12—C11—H11A 108.9
C9—C11—H11A 108.9
C12—C11—H11B 108.9
C9—C11—H11B 108.9
H11A—C11—H11B 107.8
O6—C12—C13* 103.5 (10)

C21—O2—C2—C3 114.88 (14)
C21—O2—C2—C1 −120.16 (14)
O1—C1—C2—O2 14.32 (18)
C10—C1—C2—C3 −167.98 (11)
C10—C1—C2—C1 −126.74 (15)
O1—C1—C2—C1 −171.04 (11)
C11—C9—C10—C1 68.63 (14)
C8—C9—C10—C1 −179.56 (11)
C20—C9—C10—C1 179.08 (11)
C12—C10—C11—C12 −60.11 (16)
C10—C9—C11—C12 −172.88 (12)
C17—O6—C23—H23A 109.5
O4—C23—H23A 109.5


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| Bond/Angle | Value (deg) |
|------------|------------|
| C4—C5—C10—C1 | -61.70 (13) |
| C19—C5—C10—C9 | -74.18 (14) |
| C6—C5—C10—C9 | 48.42 (15) |
| C4—C5—C10—C9 | 165.19 (11) |
| C8—C9—C11—C12 | 58.63 (15) |
| C3—C4—C18—O4 | -143.75 (13) |
| C5—C4—C18—O4 | 91.63 (15) |
| C22—O3—C21—O2 | 69.8 (2) |
| C2—O2—C21—O3 | 76.5 (2) |