Anthelmintic flavonoids and other compounds from Combretum glutinosum Perr. ex DC (Combretaceae) leaves

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Abstract: A chemical study of the hydro-ethanol extract of the leaves of Combretum glutinosum resulted in the isolation of nine compounds, including 5-demethylsinensetin (1), umuhengerin (2), (20S,24R)-ocotillone (3), luedol (4), -sitosterol (5), oleanolic acid (6), betulinic acid (7), corymbosin (8) and -sitosterol glucoside (9). Four compounds have been isolated for the first time from the genus Combretum [viz. (1), (2), (3) and (8)]. The crystal structures of flavonoid (2), C20H20O8, Z = 2, and triterpene (3), C30H50O3, Z = 1, have been determined for the first time; the latter confirmed the absolute configuration of native (20S,24R)-ocotillone previously derived from the crystal structures of related derivatives. The molecules of (3) are linked into supramolecular chains by intermolecular O—H...O hydrogen bonds. The crude extracts obtained by aqueous decoction and hydro-ethanolic maceration, as well as the nine isolated compounds, were tested for their anthelmintic activity on the larvae and adult worms of Haemonchus contortus, a hematophage that causes parasitic disorders in small ruminants. The evaluated anthelmintic activity showed that the extracts at different doses, as well as all the compounds tested at 150 µg ml−1, inhibited the migration of the larvae and the motility of the adult worms of the parasite compared with the phosphate buffer solution negative reference control. The best activity was obtained with flavonoids (1), (2) and (8) on both stages of the parasite. The flavones that showed good activity can be used for the further development of other derivatives, which could increase the anthelmintic efficacy.

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A chemical study of the hydro-ethanol extract of the leaves of *Combretum glutinosum* resulted in the isolation of nine compounds, including 5-demethyl-sinensetin (1), umuhengerin (2), (20S,24R)-ocotillone (3), lupeol (4), β-sitosterol (5), oleanolic acid (6), betulinic acid (7), corymbosin (8) and β-sitosterol glucoside (9). Four compounds have been isolated for the first time from the genus *Combretum* [viz. (1), (2), (3) and (8)]. The crystal structures of flavonoid (2), C₂₀H₂₀O₈, Z = 2, and triterpene (3), C₃₀H₅₀O₃, Z = 1, have been determined for the first time; the latter confirmed the absolute configuration of native (20S,24R)-ocotillone previously derived from the crystal structures of related derivatives. The molecules of (3) are linked into supramolecular chains by intermolecular O—H···O hydrogen bonds. The crude extracts obtained by aqueous decoction and hydro-ethanolic maceration, as well as the nine isolated compounds, were tested for their anthelmintic activity on the larvae and adult worms of *Haemonchus contortus*, a hematophage that causes parasitic disorders in small ruminants. The evaluated anthelmintic activity showed that the extracts at different doses, as well as all the compounds tested at 150 µg ml⁻¹, inhibited the migration of the larvae and the motility of the adult worms of the parasite compared with the phosphate buffer solution negative reference control. The best activity was obtained with flavonoids (1), (2) and (8) on both stages of the parasite. The flavones that showed good activity can be used for the further development of other derivatives, which could increase the anthelmintic efficacy.

1. Introduction

Combretaceae are trees, shrubs or often lianas widely distributed in subtropical to tropical regions. This family consists of 18 genera, including 370 species of *Combretum* (Malgras, 1992; McGaw *et al.*, 2001, Amadou, 2004). These species are widely used in traditional medicine for their numerous pharmacological properties (Komlan, 2002). *C. glutinosum* is a tree of the genus *Combretum* belonging to the family Combretaceae. This plant is most often present in tree savannas, normally on shallow soils (Akoègninou *et al.*, 2006). It is distributed in tropical Africa from Mauritania to Uganda, passing through, for example, Senegal, Cameroon and Chad. In Bénin, the plant is spread in the North in Kandi, Kétéou, Toukountouna, south of Malanville, Bessassi and Porga, and in the Pendrari Park (Akoègninou *et al.*, 2006). This species is among the most widely used of the medicinal plants in West Africa (Kerharo & Adam, 1974). It has been reported by Toklo *et al.* (2021) that it is used in the treatment of malaria.
dysentery, diarrhea, bronchitis and hypertension. The traditional uses of this plant have led to numerous pharmacological studies, including antibacterial, antifungal, anthelmintic, antimalarial and antiparasitic properties (Baba-Moussa et al., 1999; Ouattara et al., 2006; Usman et al., 2017; Sall et al., 2017; Alowanou et al., 2019). Previous phytochemical studies of the genus *Combretum* led to the isolation of tannins, flavonoids, triterpenoids and steroids (Jossang et al., 1994; Dawe et al., 2013; Roy et al., 2014, Amako et al., 2016; Sene et al., 2018; N’Diaye et al., 2017; Balde et al., 2019). In the search for a new active ingredient effective against increasing biological resistance to synthetic anthelmintics, the study reported here was undertaken on the leaves of *C. glutinosum*, which were obtained from plants in Bénin. The search for bioactive secondary metabolites from the leaves revealed nine known compounds (Scheme 1), of which the crystal structures of two, one flavonoid and one triterpene, have been determined for the first time. The biological activity of these compounds on the larvae and adult worms of *H. contortus*, a hematophage that causes parasitic disorders in small ruminants, has also been investigated.

2. Experimental

2.1. Chromatographic and spectroscopic analysis

Column chromatography was performed using 230–400 mesh silica gel (Merck, Darmstadt, Germany), 70–230 mesh silica gel (Merck) and sephadex LH-20 (Sigma–Aldrich). Thin-layer chromatography (TLC) was performed on a precoated aluminium sheet of silica gel 60 F254 (Merck). The spots of compounds were detected using UV lamps at two wavelengths (254 and 365 nm) and then fixed using a 10% sulfuric acid spray reagent, followed by heating to 373 K. The high-resolution mass spectra were recorded in positive mode using a QTOF mass spectrometer (Bruker, Germany) equipped with an HESI source. The spectrometer operates in positive mode (mass range 100–1500, with a scan rate of 1.00 Hz), with automatic gain control to provide high accuracy mass measurements within the mass range. NMR spectra were recorded in deuterated chloroform (CDCl3) and/or deuterated methanol (MeOD) using a Bruker DRX 500 NMR spectrometer (Bruker, Rheinstetten, Germany); the chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) (Sigma–Aldrich, Germany) as the internal standard.

2.2. Collection of plant material, extraction and isolation of compounds

The leaves of *C. glutinosum* were collected in April 2018 in Kandi (in northern Bénin) and identified at the national herbarium of the University of Abomey–Calavi. A reference specimen was stored under the accession number YH 241/HNB after authentication.

The leaves were dried in the shade for two weeks before pulverization. The leaf powder (500 g) was macerated three times in 10 l of an ethanol/water (7:3 v/v) mixture at room temperature for 72 h. After filtration, the crude extract (67 g) was obtained by evaporation of the solvent under reduced pressure using a rotary evaporator equipped with a vacuum pump. Different systems were used for TLC of the extract in order to find the best separation system. The extract was separated directly by silica-gel column chromatography. The column was eluted with mixtures of hexane–ethyl acetate (hex/EtOAc) and methanol with increasing polarity to give 92 fractions of 200 ml each. They were grouped on the basis of their TLC profile into five main fractions, i.e. FCG1 (Hex/EtOAc 10%, 5.3 g), FCG2 (Hex/EtOAc 20%, 12.9 g), FCG3 (Hex/EtOAc 30%, 5.6 g), FCG4 (Hex/EtOAc 40–50%, 5 g) and FCG5 (MeOH, 21.6 g), with one pure compound, lupeol [(4); 13 mg], obtained in the hex/EtOAc 10% system.

The FCG2 fraction was purified by silica-gel column chromatography using an isocratic system of hex/EtOAc (17:3 v/v) to give betulinic acid [(7); 35 mg], oleanolic acid [(6); 12 mg], β-sitosterol [(5); 26 mg], and (20S,24R)-ocotillone [(3); 55 mg], as well as two subfractions, FCG2-1 and FCG2-2. The FCG2-2 subfraction (2.1 g) was separated on a Sephadex LH-20 column by eluting with dichloromethane–methanol (4:6 v/v) to yield corymbosin [(8); 6 mg].

Based on the TLC profiles, the FCG2-2 subfraction was combined with the FCG3 fraction and subjected to silica-gel column chromatography using a gradient elution of hex/EtOAc with increasing polarity to obtain the compounds 5-demethylsinensetin [(1); 17 mg] and umuhengerin [(2)
Table 1
Experimental details.

For both structures: Z = 4. Experiments were carried out at 160 K with Cu Kα radiation. H atoms were treated by a mixture of independent and constrained refinement. The absorption correction was numerical based on Gaussian integration over a multifaceted crystal model (Coppens et al., 1965) plus empirical (using intensity measurements) using spherical harmonics (CrysAlis PRO; Rigaku Oxford Diffraction, 2021).

| Crystal data                  | (2)                          | (3)                          |
|-------------------------------|------------------------------|------------------------------|
| Chemical formula              | C₅₂H₄₂O₂₆                   | C₆₀H₄₂O₃                   |
| Mᵢ                           | 388.36                      | 458.70                      |
| Crystal system, space group   | Triclinic, P₃             | Orthorhombic, P₃2₁2₁       |
| a, b, c (Å)                   | 4.97902 (15), 18.5654 (5), 19.1368 (3) | 6.37386 (6), 12.10746 (11), 33.8928 (3) |
| α, β, γ (°)                   | 89.5065 (18), 84.322 (2), 89.375 (2) | 90, 90, 90                |
| V (Å³)                       | 1760.12 (8)                 | 2615.55 (4)                |
| μ (mm⁻¹)                     | 0.96                         | 0.56                        |
| Crystal size (mm)             | 0.17 × 0.03 × 0.01          | 0.24 × 0.19 × 0.05          |

Data collection

| Diffractometer                | Rigaku Oxford Diffraction XtaLAB Synergy | Oxford Diffraction SuperNova dual radiation |
|-------------------------------|------------------------------------------|---------------------------------------------|
| T min, T max                  | 0.694, 1.000                             | 0.614, 1.000                               |
| No. of measured, independent and observed | 34916, 6662, 5215                       | 26797, 5424, 5324                         |
| | [I > 2σ(I)] reflections       |                                           |                                            |
| Rint                          | 0.060                                     | 0.018                                      |
| (sin θ/λ) max (Å⁻¹)           | 0.610                                     | 0.630                                      |

Refinement

| R[F² > 2σ(F²)], wR(F²), S   | 0.047, 0.113, 1.05                      | 0.032, 0.089, 1.03                      |
| No. of reflections          | 6661                                      | 5424                                      |
| No. of parameters           | 524                                       | 310                                       |
| Δρ_max, Δρ_min (e Å⁻³)      | 0.44, -0.23                               | 0.23, -0.14                               |
| Absolute structure          | -                                          | Flack x determined using 2226 quotients |
| Absolute structure parameter| -                                          | [(F) - (F')][(F) + (F')] (Parsons et al., 2013) |
|                             | -0.07 (4)                                 |                                            |

Computer programs: CrysAlis PRO (Rigaku Oxford Diffraction, 2021), SHELXT2018 (Sheldrick, 2015a), OLEX2 (Dolomanov et al., 2009), Mercury (Macrae et al., 2020), SHELXL2018 (Sheldrick, 2015b) and PLATON (Spek, 2020).

22 mg]. The FCG4 fraction was also eluted with a mixture of ethyl acetate and 5% methanol to give eight subfractions (FCG4 1–8), which all contained an impure compound (CCG20). The FCG4-2 fraction was passed through a Sephadex LH-20 column and eluted with methanol to give solely pure CCG20, which was identified as β-sitosterol glucoside [(9); 48 mg].

Colourless needle-like crystals of (2) and colourless plate-like crystals of (3) were obtained by slow diffusion of dichloromethane into their solutions in methanol. Selected crystals were mounted on cryo loops.

2.3. Aqueous extract

An aqueous extract was obtained by boiling 100 g of C. glutinosum leaf powder in 1000 ml of distilled water brought to the boil for 30 min. After decantation, the mixture was filtered on Whatman paper and the filtrate obtained was evaporated under vacuum to obtain the dry extract.

2.4. Anthelmintic tests

2.4.1. Test for inhibition of larval migration and motility of adult worms. The test of larval migration and motility of adult worms in the presence of the samples was evaluated following the procedure of Hounzangbe-Adote et al. (2005). The observation of the worms in the presence of the extracts was done every 6 h and every 3 h in the presence of the compounds. The concentration of the tested compounds was 150 μg ml⁻¹ in phosphate buffer solution (PBS, pH 7 and 0.15 M), analogous to that used by Brunet & Hoste (2006). Levamisole and PBS were used as positive and negative reference controls, respectively.

2.4.2. Statistical analysis. The different values were included in a two-criteria repeated measures analysis of variance model. The comparison of means for the different tests was done using the SNK procedure, which runs the Student–Newman–Keuls test in the R software. Differences were considered significant at the 5% level.

2.5. Refinement

Crystal data, data collection and structure refinement details for (2) and (3) are summarized in Table 1. For both structures, the hydroxy H atoms were located in a difference Fourier map and their positions were refined freely along with individual isotropic displacement parameters. The methyl H atoms were constrained to an ideal geometry (C—H = 0.98 Å), with Uiso(H) = 1.5Ueq(C), but were allowed to rotate freely about the C—C bonds. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C—H distances of 0.95 (aromatic), 0.99 (methylen) or 1.00 Å (methylene) and with Uiso(H) = 1.2Ueq(C). The absolute configuration of (3) was determined confidently from the diffraction experiment by refinement of
the absolute structure parameter using the intensity quotients method (Parsons et al., 2013). For (2), one reflection was omitted from the final cycles of refinement because its observed intensity was much lower than the calculated value as a result of being partially obscured by the beam stop; a correction for secondary extinction was also applied.

3. Results and discussion

3.1. Identification of compounds

Repeated column chromatography of *C. glutinosum* leaf hydro-ethanol extract followed by silica-gel and sephadex LH-20 column purification yielded nine known compounds: 5-demethylsinensetin, (1) (Khazneh et al., 2016), umuhengerin, (2) (Rwagabo et al., 1988; Imbenzi et al., 2014), (20S,24R)-ocotillone, (3) (Aalbersberg et al., 1991), lupeol, (4) (Sholichin et al., 1980; Banskota et al., 2000; Balde et al., 2019), β-sitosterol, (5) (Rubinstein et al., 1976; Banskota et al., 2000), oleanolic acid, (6) (Mahato & Kundu, 1994), betulinic acid, (7) (Sholichin et al., 1980; Banskota et al., 2000), corymbosin, (8) (Çitoglu et al., 2003), and β-sitosterol glucoside, (9) (Adnyana et al., 2000) (Scheme 1). The structures of the compounds were established by interpretation of their spectroscopic data, mainly 1D NMR [¹H, ¹³C and DEPT (distortionless enhancement by polarization transfer)], 2D NMR (COSY (correlated spectroscopy), HSQC (heteronuclear single quantum coherence) and HMBC (heteronuclear multiple bond correlation)] and mass spectrometry, and by comparison with literature data. Although all of these compounds are known, compounds (1), (2), (3) and (8) have been isolated for the first time from the genus *Combretum* and the crystal structures of compounds (2) and (3), previously undetermined, have been established.

3.2. The crystal structures of (2) and (3)

The flavonoid umuhengerin, (2), was originally isolated from the leaves of *Lantana trifolia* L. (Verbenaceae) and found to display *in vitro* antibacterial and antifungal properties (Rwagabo et al., 1988). In the crystal structure of (2), there are two symmetry-independent molecules in the asymmetric unit (Fig. 1). The conformations of these molecules differ primarily in the orientations of the C6/C26 and C14/C34 methoxy groups, which are the substituents adjacent to the hydroxy group and at the 4-position of the trimethoxyphenyl ring, respectively. In the former case, these methoxy C—O torsion angles differ by 15.7 (3)°, while the rotation is 164.81 (3)° in the latter case (calculated when one molecule is overlaid with the inverted form of the other molecule, as allowed by the space-group symmetry). Apart from the methyl groups of these methoxy substituents, both flavonoid molecules are essentially planar, with r.m.s. deviations of all ring C and O atoms of 0.27 and 0.14 Å for the molecules containing atoms O1 and O21, respectively, although there may be a little bowing along the axis of the three-ring system. The dihedral angles between the individual planes of the phenyl and fused rings are 7.18 (8)° and 3.05 (8)°, respectively. The hydroxy group in each independent flavonoid molecule forms an intramolecular hydrogen bond with the adjacent carbonyl O atom (Table 2). In the crystal packing, the molecules form stacks, each of which consists of repeats of just one of the independent molecules. The molecules containing atom O1 lie tilted within an otherwise uniform column that runs parallel to the [100] direction. The molecular plane is tilted by approximately 45° with respect to the stacking direction. Nonetheless, there are no significant π—π interactions, because the ring offsets resulting from the tilting preclude significant overlap of the ring systems. The molecules containing atom O21 also stack parallel to the [100] direction in a similar 45°-tilted fashion, but the orientation of the tilted planes differs from that in the O1-containing stacks (Fig. 2); the normals to the molecular planes in the two independent stacks point in

**Table 2**

|   | D—I···A | D—I | H—I···A | D—A | D—I···A |
|---|---------|-----|---------|-----|---------|
| O5—H5···O4 | 0.89 (3) | 1.75 (3) | 2.595 (2) | 159 (3) |
| O25—H25···O24 | 0.96 (3) | 1.68 (3) | 2.591 (2) | 155 (3) |

**Figure 1**
Separate views of the two symmetry-independent molecules of (2), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by spheres of arbitrary size.
different directions. Each type of stack runs parallel to another stack of the same kind related by a centre of inversion to give a centrosymmetric double-stack pair. As the planes of the molecules in the two independent types of pairs of stacks are oriented differently, π–π interactions between the stacks are precluded and the stacks are not intertwined with one another.

The Cambridge Structural Database (CSD, Version 2020.3.0 with May 2021 update; Groom et al., 2016) contains data for six closely related flavones with hydroxy or methoxy substituents at least at the 5-, 6-, 7-, 3'- and 4'-positions. The ring systems in four of these structures are planar, with perhaps a tendency towards a slight bowing along the axis of the three-ring system, similar to that observed in (2), as seen solely from visual inspection. These structures are 5,7,4'-trihydroxy-6,3',5'-trimethoxyflavone ethyl acetate solvate (Martinez-Vazquez et al., 1993), 5,3'-dihydroxy-6,7,4'-trimethoxyflavone (Parvez et al., 2001), 5,7-dihydroxy-6,3',4'-trimethoxyflavone (Suleimenov et al., 2005) and 5,7,3',5'-trihydroxy-6,4',5'-trimethoxyflavone (Adizov et al., 2013; Turdybekov et al., 2014). In the structure of 5,6,7,2',3',4'-hexamethoxyflavone (Butler et al., 2018), the bowing within the fused rings appears to be more prominent. In the structure of 5,3'-dihydroxy-6,7,2',4',5'-pentamethoxyflavone (Al-Yahya et al., 1987), the individual planes of the phenyl and fused rings are significantly tilted from one another, with a dihedral angle of 12.23 (14); this is the only example with four substituents on the phenyl ring (three methoxy and one hydroxy).

The crystal structure of the triterpene (20S,24R)-ocotillone, (3), has one molecule in the asymmetric unit (Fig. 3). In the chosen crystal, the compound is enantiomerically pure and the absolute configuration of the molecule was determined independently by the diffraction experiment; the value of the absolute structure parameter (Parsons et al., 2013) was −0.07 (4). According to the numbering of the atoms used in the refinement model, the absolute configuration of the stereogenic C atoms of the molecule is established as follows: 5R,8R,9R,10R,13R,14R,17S,20S,24R. The isolation and identification of 20S- and 20R-ocotillones have been reported on several occasions (Bisset et al., 1966, 1967; Betancor et al., 1983; Aalbersberg et al., 1991). The isolation of the corresponding alcohol, ocohillol, appears to be mentioned for the first time by Warnhoff & Halls (1965). The absolute configuration of (20S,24R)-ocotillone was deduced from an X-ray crystal structure of a bromobenzoyl derivative of the corresponding ocohillol (Yamauchi et al., 1969). The crystal structure determination of (3) is the first time the absolute configuration has been confirmed crystallographically for the native (20S,24R)-ocotillone.

The core of the molecule of (3) consists of five rings, including four fused rings, cyclohexane rings A (atoms C1–C5/C10), B (C5–C10) and C (C8/C9/C11–C14), and cyclopentane ring D (C13–C17), plus furan ring E (O18/C20–C24) attached to the fused rings at atom C17. An isopropanol substituent is present at atom C24 of the furan ring. Thus, compound (3) is (5S,8R,9R,10R,13R,14R,17S)-2-[2-hydroxypropan-2-yl]-2-methylxolan-2-yl]-4,4,8,10,14-pentamethylen-1,2,5,6,7,9,11,12,13,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one. Rings A, B and C adopt a chair conformation, with ring A being the most distorted because of the presence of the sp2-hybridized keto C atom. The puckering parameters (Cremer

| D—H⋯A | D—H | D⋯A | D—H⋯A |
|-------|------|-----|--------|
| O25—H25—O3 | 0.90 (3) | 2.03 (3) | 2.9325 (18) | 172 (3) |

Symmetry code: (i) −x + 1, −y + 1, z − 1/2

Figure 2
The crystal packing of (2), viewed down the a axis, showing the centrosymmetric double-stack columns of molecules, with the columns at the top and bottom being composed solely of one of the symmetry-independent types of molecules and the columns on the left and right being composed solely of the other independent type.

Figure 3
View of the molecule of (3), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by spheres of arbitrary size.
& Pople, 1975) for ring A are $\theta = 15.82 (18)^\circ$ and $\varphi = 322.1 (7)^\circ$ for the atom sequence C1—C2—C3—C4—C5—C10. For ring B, $\theta = 11.01 (15)^\circ$ and $\varphi = 17.2 (8)^\circ$ for the atom sequence C5—C6—C7—C8—C9—C10 and for ring C, $\theta = 6.30 (15)^\circ$ and $\varphi = 8.5 (13)^\circ$ for the atom sequence C8—C9—C11—C12—C13—C14. Ring D has a near-ideal half-chair conformation twisted on C13—C14 [$\varphi_2 = 197.8 (4)^\circ$ for the atom sequence C13—C14—C15—C16—C17], while ring E has a slightly distorted envelope conformation with atom O20 as the envelope flap [$\varphi_2 = 188.6 (4)^\circ$ for the atom sequence O20—C21—C22—C23—C24]. The A/B, B/C and C/D ring junctions are all trans-fused to each other along the C5—C10, C8—C9 and C13—C14 bonds, respectively. This brings the methyl groups at C8 and C10 into cis positions, while the methyl groups at C8 and C14 are trans to one another. The furan substituent at the cyclopropane ring lies trans to the C14 methyl group.

Intermolecular O—H···O hydrogen bonds involving the hydroxy group and the ketone O atom link the molecules into extended wave-like chains (Table 3 and Fig. 4), which run parallel to the [001] direction and can be described by a graph-set motif (Bernstein et al., 1995) of (C(16)).

3.3. Anthelmintic activity

3.3.1. About the extracts. The crude extracts obtained by aqueous decoction and hydro-ethanolic maceration, as well as the nine isolated compounds, were tested for their anthelmintic activity on the larval and adult worms of H. contortus. The larval migration inhibition technique applied is based on the measurement of the migration rate of parasite larvae through a membrane after contact with the tested extract. At different doses, aqueous and hydro-ethanolic extracts of C. glutinosum significantly inhibited in vitro larval migration of H. contortus ($p < 0.001$) (Fig. 5). This effect is independent of the dose and does not vary with the extraction solvent ($p > 0.05$). However, the aqueous extract appeared to be more effective than the hydro-ethanolic extract (Fig. 5). Similarly, both extracts significantly reduced the motility of adult H. contortus worms ($p < 0.001$). Although the inhibition effect did not vary with dose and extraction solvent ($p > 0.05$), it did vary with time ($p < 0.001$) and, paradoxically, the hydro-ethanolic extract appeared to inhibit adult worm motility more (Table 4).

In order to know the chemical composition of these two extracts for the identification of the active principle, the present work was continued with the hydro-ethanolic extract and the compounds isolated therefrom were tested on H. contortus larvae and worms.

3.3.2. On the compounds. In vitro, the effect of the compounds was evaluated on H. contortus larvae and adult worms. All the compounds inhibited the migration of H. contortus larvae (Fig. 6) and the three isolated flavonoids seem to present the best results with inhibition percentages of 75.37, 53.26 and 47.73%, respectively, for compounds (1), (2) and (8), although they are all less active than the reference drug levamisol (95.97%). For the adult worms observed every 3 h with a magnifying glass after their contact with the tested compounds, the total inhibition of their motility was observed with the positive reference control (levamisol) after just 3 h of exposure. This inhibition was total at 12 h with compounds (1), (2), (4), (5) and (8). On the other hand, in phosphate buffer solution (PBS), 75% of adult worms were still mobile after 18 h (Table 5). Statistical analysis showed that the compounds inhibited the larval migration and motility of H. contortus

Table 4

| Sample            | Concentration (dose, $\mu$g ml$^{-1}$) | Time |
|-------------------|---------------------------------------|------|
|                   |                                       | 6 h  | 12 h | 18 h | 24 h | 30 h |
| PBS               |                                       | 100  | 100  | 66.7 | 33.3 | 0    |
| Levamisol         |                                       | 100  | 100  | 0    | 0    | 0    |
| Aqueous extract   |                                       | 100  | 100  | 50   | 0    | 0    |
| Ethanol/water     |                                       | 100  | 100  | 50   | 0    | 0    |
|                   |                                       | 50   | 50   | 50   | 50   | 50   |
|                   |                                       | 66.7 | 66.7 | 66.7 | 66.7 | 66.7 |
|                   |                                       | 0    | 50   | 50   | 50   | 50   |
|                   |                                       | 100  | 100  | 50   | 50   | 50   |
|                   |                                       | 100  | 100  | 50   | 50   | 50   |
|                   |                                       | 100  | 100  | 50   | 50   | 50   |

Figure 4

The crystal packing of (3), viewed down the b axis, showing the O—H···O hydrogen bonds (magenta dashed lines) linking the molecules into wave-like chains. Most H atoms have been omitted for clarity.
adult worms within the same time as levamisole, compared with the negative control \( (p < 0.001) \). On adult worms, the inhibitory effect varied with time \( (p < 0.001) \) and flavonoids; in particular, 5-demethylsinensetin, (1), would be responsible for the known anthelmintic activity of the plant.

Indeed, the class of polyphenols is strongly suspected as being the active agent in the anthelmintic effect of plants (Ayers et al., 2008). Condensed tannins are frequently reported as being responsible for such effects, for example, in the report by Hoste et al. (2018). Nonetheless, other reports do link anthelmintic properties to flavonoids (Paolini et al., 2003; Barrau et al., 2005). Given the results of the in vivo tests, the known anthelmintic activity of C. glutinosum appears to be related to the presence of the flavonoids isolated from this plant. Thus, following the report that C. glutinosum is an anthelmintic plant (Alowanou et al., 2019), the present study has allowed the anthelmintic capacity of the different compounds isolated from this plant to be ranked and highlighted. It appears that these compounds, although less active than the positive reference control, have a larvicidal and vermicidal effect on H. contortus, with 5-demethylsinensetin, (1), being the most active. The decrease in the migration of infesting larvae and the reduction of the motility of adult worms could disrupt their settlement in the mucosal wall of the digestive tract and thus ensure their progressive elimination from the infested animal (Dedehou et al., 2014). These results could serve as a basis for a conformational analysis leading to the proposal of a new compound with a broader spectrum of activity than current commercially available anthelmintics.

### 4. Conclusion

The phytochemical investigation of the leaves of C. glutinosum led to the isolation of nine known compounds, which were characterized using spectroscopic analyses and by comparison with literature data. The crystal structures of two compounds were described for the first time in the present work and four compounds have been isolated for the first time from the genus Combretum. The flavonoids isolated from the plant presented the best in vitro activity on H. contortus. The results of this study could be verified in vivo on sheep in order to gain further insight into and enhance the status of this plant.

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**Anthelmintic flavonoids and other compounds from *Combretum glutinosum* Perr. ex DC (Combretaceae) leaves**

Placide M. Toklo, Eléonore Yayi Ladekan, Anthony Linden, Sylvie Hounzangbe-Adote, Siméon F. Kouam and Joachim D. Gbenou

Computing details

For both structures, data collection: *CrysAlis PRO* (Rigaku Oxford Diffraction, 2021); cell refinement: *CrysAlis PRO* (Rigaku Oxford Diffraction, 2021); data reduction: *CrysAlis PRO* (Rigaku Oxford Diffraction, 2021); program(s) used to solve structure: *SHELXT2018* (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2018* (Sheldrick, 2015b); molecular graphics: OLEX2 (Dolomanov *et al.*, 2009) and *Mercury* (Macrae *et al.*, 2020); software used to prepare material for publication: *SHELXL2018* (Sheldrick, 2015b) and *PLATON* (Spek, 2020).

5-Hydroxy-6,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chromen-4-one (2)

*Crystal data*

| Symbol | Value | Value | Value |
|---|---|---|---|
| C₂₀H₂₀O₈ | | | |
| Mᵣ | 388.36 | | |
| Triclinic, P₁ | | | |
| a | 4.97902 (15) Å | | |
| b | 18.5654 (5) Å | | |
| c | 19.1368 (3) Å | | |
| α | 89.5065 (18)° | | |
| β | 84.322 (2)° | | |
| γ | 89.375 (2)° | | |
| V | 1760.12 (8) Å³ | | |
| Z | 4 | | |

*Data collection*

| Rigaku Oxford Diffraction XtaLAB Synergy | | |
| dual radiation | | |
| diffractometer | | |
| Radiation source: micro-focus sealed X-ray tube, PhotonJet (Cu) X-ray source | | |
| Mirror monochromator | | |
| Detector resolution: 5.81 pixels mm⁻¹ | | |
| ω scans | | |

Absorption correction: gaussian

Numerical absorption correction based on Gaussian integration over a multifaceted crystal model (Coppens *et al.*, 1965) plus an empirical (using intensity measurements) absorption correction using spherical harmonics (*CrysAlis PRO*; Rigaku Oxford Diffraction, 2021)

| Tmin | 0.694 | |
| Tmax | 1.000 | |
| 34916 measured reflections | | |
| 6662 independent reflections | | |
| 5215 reflections with I > 2σ(I) | | |
| Rint | 0.060 | |
| θmax | 70.1° | |
| θmin | 3.3° | |
| h | -6→6 | |
| k | -22→22 | |
| l | -23→22 | |
Refinement

Refinement on $F^2$
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.047$
$wR(F^2) = 0.113$
$S = 1.05$
6661 reflections
524 parameters
0 restraints
Primary atom site location: dual
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
$w = 1/\left[\sigma^2(F_o^2) + (0.0439P)^2 + 0.954P\right]$
where $P = (F_o^2 + 2F_c^2)/3$
$\Delta/\sigma$ max = 0.001
$\Delta\rho$ max = 0.44 e Å$^{-3}$
$\Delta\rho$ min = −0.23 e Å$^{-3}$
Extinction correction: SHELXL2018 (Sheldrick, 2015b), $F_c^* = kF_c[1 + 0.001xF_c^2\lambda^3/\sin(2\theta)]^{1/4}$
Extinction coefficient: 0.00064 (15)

Special details

Experimental. Data collection and full structure determination done by Prof. Anthony Linden: anthony.linden@chem.uzh.ch
The financial support from the Swiss National Science Foundation (R’Equip grant no. 206021_164018) and the University of Zurich for the purchase of the X-ray diffractometer used in this work is gratefully acknowledged.
Solvent used: dichloromethane / MeOH Cooling Device: Oxford Cryosystems Cryostream 800 Crystal mount: on a cryo-loop Frames collected: 5692 Seconds exposure per frame: 3.5-14.0 Degrees rotation per frame: 0.5 Crystal-detector distance (mm): 32.0 Client: Placide Toklo Sample code: G10 (L2102)

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

Refinement. There are two symmetry-independent molecules in the asymmetric unit. Their conformations differ mainly in the orientations of the C6/C26 and C14/C34 methoxy groups.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\AA^2$)

|    | x     | y     | z     | $U_{iso}^*/U_{eq}$ |
|----|-------|-------|-------|-------------------|
| O1 | 0.8422 (3) | 0.85801 (7) | 0.42135 (7) | 0.0221 (3) |
| O4 | 1.3522 (3) | 1.02957 (7) | 0.40490 (7) | 0.0257 (3) |
| O5 | 1.1747 (3) | 1.06246 (8) | 0.28553 (8) | 0.0273 (3) |
| H5 | 1.259 (6) | 1.06116 (16) | 0.3243 (16) | 0.052 (9)* |
| O6 | 0.8350 (3) | 1.03119 (7) | 0.18570 (7) | 0.0259 (3) |
| O7 | 0.5323 (3) | 0.91317 (8) | 0.19914 (7) | 0.0278 (3) |
| O13 | 0.6742 (3) | 0.63636 (8) | 0.56501 (8) | 0.0324 (4) |
| O14 | 0.9692 (3) | 0.64850 (8) | 0.67492 (7) | 0.0280 (3) |
| O15 | 1.2499 (3) | 0.76492 (8) | 0.69432 (7) | 0.0264 (3) |
| C2 | 1.0127 (4) | 0.87011 (10) | 0.47147 (9) | 0.0197 (4) |
| C3 | 1.1858 (4) | 0.92593 (11) | 0.46730 (10) | 0.0222 (4) |
| H3 | 1.302837 | 0.931941 | 0.503074 | 0.027* |
| C4 | 1.1959 (4) | 0.97653 (10) | 0.40948 (10) | 0.0205 (4) |
| C4A | 1.0182 (4) | 0.96151 (10) | 0.35638 (10) | 0.0199 (4) |
| C5 | 1.0124 (4) | 1.00467 (10) | 0.29491 (10) | 0.0216 (4) |
| C6 | 0.8454 (4) | 0.98775 (10) | 0.24420 (10) | 0.0219 (4) |
| C7 | 0.6810 (4) | 0.92629 (11) | 0.25317 (10) | 0.0227 (4) |
| C8 | 0.6811 (4) | 0.88307 (11) | 0.31284 (10) | 0.0220 (4) |
| Atom | x     | y     | z     | Ueq  |
|------|-------|-------|-------|------|
| H8   | 0.569965 | 0.841766 | 0.318877 | 0.026* |
| C8A  | 0.8482 (4) | 0.90209 (10) | 0.36319 (10) | 0.0202 (4) |
| C9   | 1.0055 (5) | 1.00522 (12) | 0.12617 (11) | 0.0323 (5) |
| H91  | 0.992408 | 1.037996 | 0.086210 | 0.048* |
| H92  | 0.947640 | 0.957036 | 0.113962 | 0.048* |
| H93  | 1.192845 | 1.002897 | 0.137705 | 0.048* |
| C10  | 0.3684 (4) | 0.84999 (11) | 0.20370 (11) | 0.0280 (5) |
| H101 | 0.283392 | 0.844604 | 0.160018 | 0.042* |
| H102 | 0.228375 | 0.854585 | 0.243201 | 0.042* |
| C11  | 0.9878 (4) | 0.81357 (10) | 0.52674 (10) | 0.0205 (4) |
| C12  | 0.8257 (4) | 0.75395 (11) | 0.51883 (10) | 0.0229 (4) |
| H12  | 0.722807 | 0.751012 | 0.479732 | 0.028* |
| C13  | 0.8161 (4) | 0.69871 (11) | 0.56883 (10) | 0.0246 (4) |
| C14  | 0.9623 (4) | 0.70409 (10) | 0.62693 (10) | 0.0218 (4) |
| C15  | 1.1193 (4) | 0.76461 (11) | 0.63504 (10) | 0.0211 (4) |
| H16  | 1.244991 | 0.860170 | 0.589721 | 0.026* |
| C17  | 0.5090 (5) | 0.63036 (13) | 0.50876 (12) | 0.0356 (5) |
| H171 | 0.622361 | 0.632223 | 0.463913 | 0.053* |
| H172 | 0.377958 | 0.670236 | 0.510834 | 0.053* |
| H173 | 0.413018 | 0.584477 | 0.512823 | 0.053* |
| C18  | 0.7326 (5) | 0.64279 (12) | 0.72304 (11) | 0.0326 (5) |
| H181 | 0.577442 | 0.632168 | 0.697239 | 0.049* |
| H182 | 0.700503 | 0.688358 | 0.748115 | 0.049* |
| H183 | 0.757423 | 0.603916 | 0.756847 | 0.049* |
| C19  | 1.4212 (4) | 0.82473 (11) | 0.70315 (11) | 0.0269 (4) |
| H191 | 1.563147 | 0.826701 | 0.663895 | 0.040* |
| H192 | 1.503526 | 0.819113 | 0.747337 | 0.040* |
| C193 | 1.314256 | 0.869417 | 0.704262 | 0.040* |
| O21  | 0.6336 (3) | 0.41743 (7) | 0.14003 (7) | 0.0228 (3) |
| O24  | 0.1754 (3) | 0.40137 (8) | −0.02513 (7) | 0.0293 (3) |
| O25  | 0.3923 (3) | 0.27616 (8) | −0.05320 (7) | 0.0304 (3) |
| H25  | 0.277 (7) | 0.3183 (18) | −0.0513 (16) | 0.060 (9)* |
| O26  | 0.7475 (3) | 0.16941 (8) | −0.01936 (7) | 0.0274 (3) |
| O27  | 1.0071 (3) | 0.18272 (7) | 0.09442 (7) | 0.0255 (3) |
| O33  | 0.7591 (3) | 0.57926 (8) | 0.33934 (7) | 0.0285 (3) |
| O34  | 0.4623 (3) | 0.69559 (8) | 0.32162 (7) | 0.0277 (3) |
| O35  | 0.1347 (3) | 0.70599 (8) | 0.21774 (7) | 0.0291 (3) |
| C22  | 0.4571 (4) | 0.47098 (10) | 0.12585 (10) | 0.0222 (4) |
| C23  | 0.3019 (4) | 0.46705 (10) | 0.07207 (10) | 0.0227 (4) |
| H23  | 0.180196 | 0.505462 | 0.064500 | 0.027* |
| C24  | 0.3164 (4) | 0.40596 (11) | 0.02590 (10) | 0.0237 (4) |
| C24A | 0.5018 (4) | 0.34887 (11) | 0.04278 (10) | 0.0227 (4) |
| C25  | 0.5328 (4) | 0.28491 (11) | 0.00271 (10) | 0.0235 (4) |
| C26  | 0.7070 (4) | 0.23045 (11) | 0.02062 (10) | 0.0234 (4) |
| C27  | 0.8500 (4) | 0.23940 (11) | 0.07986 (10) | 0.0226 (4) |
| C28  | 0.8242 (4) | 0.30238 (11) | 0.11937 (10) | 0.0235 (4) |
sup-4

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|    | x     | y     | z     | U11   | U22   | U33   | U12   | U13   | U23   |
|----|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| O1 | 0.0252 (7) | 0.0241 (7) | 0.0172 (6) | -0.0027 (6) | -0.0031 (5) | 0.0053 (5) |
| O4 | 0.0301 (8) | 0.0240 (7) | 0.0230 (7) | -0.0068 (6) | -0.0027 (6) | 0.0032 (6) |
| O5 | 0.0336 (8) | 0.0245 (7) | 0.0242 (7) | -0.0066 (6) | -0.0048 (6) | 0.0068 (6) |
| O6 | 0.0328 (8) | 0.0246 (7) | 0.0200 (7) | 0.0032 (6) | -0.0023 (6) | 0.0068 (6) |
| O7 | 0.0326 (8) | 0.0292 (8) | 0.0228 (7) | -0.0061 (6) | -0.0088 (6) | 0.0040 (6) |
| O13| 0.0427 (9) | 0.0273 (8) | 0.0282 (8) | -0.0129 (7) | -0.0071 (7) | 0.0029 (6) |
| O14| 0.0317 (8) | 0.0240 (7) | 0.0269 (7) | 0.0011 (6) | 0.0020 (6) | 0.0105 (6) |
| O15| 0.0323 (8) | 0.0267 (7) | 0.0209 (7) | -0.0050 (6) | -0.0066 (6) | 0.0072 (6) |
| C2 | 0.0208 (10) | 0.0233 (10) | 0.0145 (9) | 0.0033 (8) | 0.0000 (7) | 0.0009 (7) |
| C3 | 0.0250 (10) | 0.0241 (10) | 0.0172 (9) | 0.0000 (8) | -0.0009 (8) | 0.0015 (8) |
| C4 | 0.0210 (10) | 0.0209 (10) | 0.0189 (9) | 0.0014 (8) | 0.0017 (8) | -0.0010 (7) |
| C4A| 0.0206 (10) | 0.0207 (9) | 0.0177 (9) | 0.0021 (7) | 0.0002 (7) | 0.0010 (7) |
| C5 | 0.0253 (10) | 0.0172 (9) | 0.0216 (9) | 0.0007 (8) | 0.0018 (8) | 0.0014 (7) |
| C6 | 0.0254 (10) | 0.0221 (10) | 0.0178 (9) | 0.0032 (8) | -0.0005 (8) | 0.0032 (7) |
Geometric parameters (Å, °)

|   |   |   |   |   |   |
|---|---|---|---|---|---|
|   |   |   |   |   |   |
| C1 | C2 | 1.364 (2) | O1 | O21 | O22 |
| C1 | C8A | 1.374 (2) | O1 | O21 | O22 |
| O1 | C2 | 1.259 (2) | O21 | O22 | O22 |

supporting information
| Bond                  | Distance (Å) | Bond                  | Distance (Å) |
|----------------------|--------------|----------------------|--------------|
| O5—C5                | 1.350 (2)    | O25—C25              | 1.347 (2)    |
| O5—H5                | 0.89 (3)     | O25—H25              | 0.96 (3)     |
| O6—C6                | 1.379 (2)    | O26—C26              | 1.375 (2)    |
| O6—C9                | 1.435 (3)    | O26—C29              | 1.436 (3)    |
| O7—C7                | 1.355 (2)    | O27—C27              | 1.348 (2)    |
| O7—C10               | 1.433 (3)    | O27—C30              | 1.431 (2)    |
| O13—C13              | 1.369 (2)    | O33—C33              | 1.375 (2)    |
| O13—C17              | 1.424 (3)    | O33—C37              | 1.423 (3)    |
| O14—C14              | 1.378 (2)    | O34—C34              | 1.366 (2)    |
| O14—C18              | 1.426 (3)    | O34—C38              | 1.437 (3)    |
| O15—C15              | 1.363 (2)    | O35—C35              | 1.356 (2)    |
| O15—C19              | 1.428 (3)    | O35—C39              | 1.432 (3)    |
| C2—C3                | 1.352 (3)    | C22—C23              | 1.350 (3)    |
| C2—C11               | 1.481 (3)    | C22—C31              | 1.481 (3)    |
| C3—C4                | 1.443 (3)    | C23—C24              | 1.441 (3)    |
| C3—H3                | 0.9500       | C23—H23              | 0.9500       |
| C4—C4A               | 1.443 (3)    | C24—C24A             | 1.453 (3)    |
| C4A—C8A              | 1.395 (3)    | C24A—C28A            | 1.381 (3)    |
| C4A—C5               | 1.420 (3)    | C24A—C25             | 1.418 (3)    |
| C5—C6                | 1.379 (3)    | C25—C26              | 1.388 (3)    |
| C6—C7                | 1.411 (3)    | C26—C27              | 1.409 (3)    |
| C7—C8                | 1.390 (3)    | C27—C28              | 1.396 (3)    |
| C8—C8A               | 1.384 (3)    | C28—C28A             | 1.384 (3)    |
| C8—H8                | 0.9500       | C28—H28              | 0.9500       |
| C9—H91               | 0.9800       | C29—H291             | 0.9800       |
| C9—H92               | 0.9800       | C29—H292             | 0.9800       |
| C9—H93               | 0.9800       | C29—H293             | 0.9800       |
| C10—H101             | 0.9800       | C30—H301             | 0.9800       |
| C10—H102             | 0.9800       | C30—H302             | 0.9800       |
| C10—H103             | 0.9800       | C30—H303             | 0.9800       |
| C11—C16              | 1.394 (3)    | C31—C36              | 1.384 (3)    |
| C11—C12              | 1.395 (3)    | C31—C32              | 1.410 (3)    |
| C12—C13              | 1.395 (3)    | C32—C33              | 1.391 (3)    |
| C12—H12              | 0.9500       | C32—H32              | 0.9500       |
| C13—C14              | 1.392 (3)    | C33—C34              | 1.395 (3)    |
| C14—C15              | 1.394 (3)    | C34—C35              | 1.410 (3)    |
| C15—C16              | 1.393 (3)    | C35—C36              | 1.387 (3)    |
| C16—H16              | 0.9500       | C36—H36              | 0.9500       |
| C17—H171             | 0.9800       | C37—H371             | 0.9800       |
| C17—H172             | 0.9800       | C37—H372             | 0.9800       |
| C17—H173             | 0.9800       | C37—H373             | 0.9800       |
| C18—H181             | 0.9800       | C38—H381             | 0.9800       |
| C18—H182             | 0.9800       | C38—H382             | 0.9800       |
| C18—H183             | 0.9800       | C38—H383             | 0.9800       |
| C19—H191             | 0.9800       | C39—H391             | 0.9800       |
| C19—H192             | 0.9800       | C39—H392             | 0.9800       |
| C19—H193             | 0.9800       | C39—H393             | 0.9800       |
C2—O1—C8A   119.99 (15) C22—O21—C28A   119.46 (15)
C5—O5—H5    102 (2) C25—O25—H25    102.5 (19)
C6—O6—C9    112.55 (15) C26—O26—C29    113.59 (16)
C7—O7—C10   117.56 (15) C27—O27—C30    117.56 (15)
C13—O13—C17 117.24 (16) C33—O33—C37   117.01 (16)
C14—O14—C18 114.50 (16) C34—O34—C38   115.63 (17)
C15—O15—C19 116.81 (15) C35—O35—C39   116.94 (16)
C3—C2—O1    122.21 (17) C23—C22—O21   122.18 (17)
C3—C2—C11   126.43 (18) C23—C22—C31   126.15 (18)
O1—C2—C11   111.31 (17) O21—C22—C31  111.65 (17)
O1—C2—O1    112.2 (17) C23—C22—C31  126.15 (18)
C5—C4—C3    121.18 (18) C22—C23—C24  121.52 (19)
C4—C3—H3    119.4  C22—C23—H23  119.2
C4—C3—H3    119.4  C24—C23—H23  119.2
O4—C4—C3    122.45 (18) O24—C24—C23  122.70 (19)
O4—C4—C4A   122.08 (17) O24—C24—C24A  121.89 (18)
O6—C9—H91   109.5  O26—C26—C27  119.84 (18)
O6—C9—H92   109.5  O27—C27—C28  118.87 (18)
H91—C9—H92  109.5  O27—C27—C26  124.22 (18)
O6—C9—H93   109.5  O27—C27—C26  114.54 (17)
H91—C9—H93  109.5  C28—C27—C26  121.24 (18)
H92—C9—H93  109.5  C28—C27—C26  118.23 (18)
C8A—C8—H8   121.0  C28—C27—C26  120.9
C8A—C8—H8   121.0  C27—C28—H28  120.9
C12—C11—C2  119.61 (17)  C32—C31—C22  119.32 (18)
C13—C12—C11  119.40 (19)  C33—C32—C31  119.15 (19)
C13—C12—H12  120.3  C33—C32—H32  120.4
C11—C12—H12  120.3  C31—C32—H32  120.4
O13—C13—C14  115.32 (17)  O33—C33—C32  124.41 (19)
O13—C13—C12  124.60 (19)  O33—C33—C34  115.10 (17)
C14—C13—C12  120.07 (19)  C32—C33—C34  120.49 (19)
O14—C14—C13  118.58 (18)  O34—C34—C33  118.92 (18)
C13—C14—C15  120.03 (17)  C33—C34—C32  121.41 (18)
O15—C15—C16  124.40 (18)  C35—C34—C32  119.54 (18)
O15—C15—C14  115.18 (17)  C35—C34—C36  124.79 (19)
C16—C15—C14  120.42 (18)  C36—C35—C34  115.04 (17)
C15—C16—C11  119.13 (19)  C31—C36—C35  120.17 (19)
C15—C16—H16  120.4  C31—C36—H36  119.93 (19)
C11—C16—H16  120.4  C35—C36—H36  120.0
O13—C17—H171  109.5  O33—C37—H371  109.5
O13—C17—H172  109.5  O33—C37—H372  109.5
H171—C17—H172  109.5  H371—C37—H372  109.5
O13—C17—H173  109.5  O33—C37—H373  109.5
H171—C17—H173  109.5  H371—C37—H373  109.5
H172—C17—H173  109.5  H372—C37—H373  109.5
O14—C18—H181  109.5  O34—C38—H381  109.5
O14—C18—H182  109.5  O34—C38—H382  109.5
H181—C18—H182  109.5  H381—C38—H382  109.5
O14—C18—H183  109.5  O34—C38—H383  109.5
H181—C18—H183  109.5  H381—C38—H383  109.5
H182—C18—H183  109.5  H382—C38—H383  109.5
O15—C19—H191  109.5  O35—C39—H391  109.5
O15—C19—H192  109.5  O35—C39—H392  109.5
H191—C19—H192  109.5  H391—C39—H392  109.5
O15—C19—H193  109.5  O35—C39—H393  109.5
H191—C19—H193  109.5  H391—C39—H393  109.5
H192—C19—H193  109.5  H392—C39—H393  109.5
C8A—O1—C2—C3  1.9 (3)  C28A—O21—C22—C23  −1.5 (3)
C8A—O1—C2—C11 −175.76 (16)  C28A—O21—C22—C31  177.03 (16)
O1—C2—C3—C4  0.9 (3)  C21—C22—C23—C24 −0.7 (3)
C11—C2—C3—C4  178.19 (18)  C31—C22—C23—C24 −179.03 (18)
C2—C3—C4—C4A −2.3 (3)  C22—C23—C24—O24 −179.26 (19)
O4—C4—C4A—C8A  179.86 (18)  C22—C23—C24—C24A  1.8 (3)
C3—C4—C4A—C8A  1.0 (3)  C21—C22—C23—C24 −179.74 (19)
O4—C4—C4A—C5  1.4 (3)  C24—C24A—C25 −0.2 (3)
C3—C4—C4A—C5  −177.49 (18)  C23—C24—C24A—C25  178.72 (18)
C8A—C4A—C5—O5  −179.46 (17)  C28A—C24A—C25—O25 −179.38 (18)
C4—C4A—C5—O5 −1.0 (3)  C24—C24A—C25—O25  1.1 (3)
C8A—C4A—C5—C6 −0.3 (3)  C28A—C24A—C25—C26  0.9 (3)
|                  |                  |                  |                  |
|------------------|------------------|------------------|------------------|
| C4—C4A—C5—C6   | 178.22 (18)      | C24—C24A—C25—C26 | -178.69 (19)     |
| C9—O6—C6—C5    | 96.8 (2)         | C29—O26—C26—C25 | -81.1 (2)        |
| C9—O6—C6—C7    | -84.3 (2)        | C29—O26—C26—C27 | 100.8 (2)        |
| O5—C5—C6—O6    | -2.8 (3)         | O25—C25—C26—O26 | 2.9 (3)          |
| C4A—C5—C6—O6   | 178.01 (17)      | C24A—C25—C26—O26 | -177.32 (18)     |
| C4A—C5—C6—C7   | -0.8 (3)         | C24A—C25—C26—C27 | -178.96 (18)     |
| C10—O7—C7—C8   | 177.71 (17)      | C24A—C25—C26—C27 | 0.8 (3)          |
| O6—C6—C7—O7    | 3.4 (3)          | C30—O27—C27—C28 | -1.1 (3)         |
| C9—O6—C6—C7    | -177.72 (17)     | C30—O27—C27—C28 | 179.43 (17)      |
| O5—C5—C6—C7    | -178.36 (17)     | O26—C26—C27—O27 | -4.0 (3)         |
| O5—C5—C6—O6    | -2.8 (3)         | O26—C26—C27—C28 | 177.90 (18)      |
| C4A—C5—C6—C7   | -177.77 (17)     | O26—C26—C27—C28 | 176.58 (18)      |
| C5—C6—C7—C8    | 1.1 (3)          | C25—C26—C27—C28 | -1.6 (3)         |
| O7—C7—C8—C8A   | 178.50 (18)      | O27—C27—C28—C28A | -178.78 (18)     |
| C6—C7—C8—C8A   | -0.2 (3)         | C26—C27—C28—C28A | 0.6 (3)          |
| C2—O1—C8A—C8   | 175.87 (17)      | C25—C24A—C28A—C28 | -1.9 (3)        |
| C2—O1—C8A—C4A  | -3.2 (3)         | C24—C24A—C28A—C28 | 177.69 (19)     |
| C7—C8—C8A—O1   | 179.96 (17)      | C25—C24A—C28A—O21 | 179.13 (17)     |
| C7—C8—C8A—C4A  | -1.0 (3)         | C24—C24A—C28A—O21 | -1.3 (3)        |
| C5—C4A—C8A—O1  | -179.78 (16)     | C27—C28A—C28A—C24A | 1.1 (3)        |
| C5—C4A—C8A—O1  | 1.7 (3)          | C27—C28A—C28A—O21 | -179.81 (17)    |
| C5—C4A—C8A—C8  | 1.2 (3)          | C22—O21—C28A—C28A | 2.5 (3)         |
| C4—C4A—C8A—C8  | -177.30 (18)     | C22—O21—C28A—C28A | -176.54 (17)    |
| C3—C2—C11—C16  | 6.3 (3)          | C23—C22—C31—C36 | -1.8 (3)        |
| O1—C2—C11—C16  | -176.16 (16)     | C21—C22—C31—C36 | 179.73 (17)     |
| O1—C2—C11—C12  | -171.25 (19)     | C23—C22—C31—C32 | 176.7 (2)       |
| O1—C2—C11—C12  | 6.3 (2)          | C21—C22—C31—C32 | -1.8 (2)        |
| C16—C11—C12—C13| -1.5 (3)         | C36—C31—C32—C33 | 0.7 (3)         |
| C2—C11—C12—C13| 176.03 (18)      | C22—C31—C32—C33 | -177.84 (18)    |
| C17—O13—C13—C14| 176.33 (19)      | C37—O33—C33—C32 | -4.7 (3)        |
| C17—O13—C13—C12| -5.1 (3)         | C37—O33—C33—C34 | 175.24 (18)     |
| C11—C12—C13—O13| -176.99 (19)     | C31—C32—C33—O33 | 178.34 (18)     |
| C11—C12—C13—C14| 1.6 (3)          | C31—C32—C33—C34 | -1.6 (3)        |
| C18—O14—C14—C13| -77.4 (2)        | C38—O34—C34—C33 | -117.8 (2)      |
| C18—O14—C14—C15| 106.7 (2)        | C38—O34—C34—C35 | 66.5 (2)        |
| O13—C13—C14—O14| 2.6 (3)          | O33—C33—C34—O34 | 5.5 (3)         |
| C12—C13—C14—O14| -176.11 (18)     | C32—C33—C34—O34 | -174.62 (18)    |
| O13—C13—C14—C15| 178.42 (18)      | O33—C33—C34—C35 | -178.68 (17)    |
| C12—C13—C14—C15| -0.3 (3)         | C32—C33—C34—C35 | 1.2 (3)         |
| C19—O15—C15—C16| -2.3 (3)         | C39—O35—C35—C36 | -1.7 (3)        |
| C19—O15—C15—C14| 177.64 (17)      | C39—O35—C35—C34 | 178.13 (18)     |
| O14—C14—C15—O15| -5.2 (3)         | O34—C34—C35—O35 | -4.1 (3)        |
| C13—C14—C15—O15| 178.89 (17)      | O34—C34—C35—C36 | -179.81 (18)    |
| O14—C14—C15—C16| 174.79 (17)      | O34—C34—C35—C36 | 175.76 (18)     |
| C13—C14—C15—C16| -12.3 (3)        | C33—C34—C35—C36 | 0.0 (3)         |
| O15—C15—C16—C11| -178.80 (18)     | C32—C31—C36—C35 | 0.6 (3)         |
| C14—C15—C16—C11| 1.3 (3)          | C22—C31—C36—C35 | 179.06 (18)     |
| C12—C11—C16—C15| 0.1 (3)          | O35—C35—C36—C31 | 178.90 (19)     |
C2—C11—C16—C15 −177.44 (17) C34—C35—C36—C31 −0.9 (3)

Hydrogen-bond geometry (Å, °)

| D—H···A   | D—H | H···A | D···A | D—H···A |
|-----------|------|-------|-------|---------|
| O5—H5···O4 | 0.89 (3) | 1.75 (3) | 2.595 (2) | 159 (3) |
| O25—H25···O24 | 0.96 (3) | 1.68 (3) | 2.591 (2) | 155 (3) |

(5R,8R,9R,10R,13R,14R,17S)-17-[(25S,5R)-5-(2-Hydroxypropan-2-yl)-2-methyloxolan-2-yl]-4,8,10,14-pentamethyl-1,2,5,6,7,9,11,12,13,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one (3)

Crystal data

C₃₀H₅₀O₃
Mᵣ = 458.70
Orthorhombic, P2₁2₁2₁
a = 6.37386 (6) Å
b = 12.10746 (11) Å
c = 33.8928 (3) Å
V = 2615.55 (4) Å³
Z = 4
F(000) = 1016

Data collection

Oxford Diffraction SuperNova dual radiation diffractometer
Radiation source: micro-focus sealed X-ray tube, SuperNova (Cu) X-ray source
Mirror monochromator
Detector resolution: 10.3801 pixels mm⁻¹
ω scans

Absorption correction: gaussian
Numerical absorption correction based on gaussian integration over a multifaceted crystal model (Coppens et al., 1965) plus an empirical (using intensity measurements) absorption correction using spherical harmonics (CrysAlis PRO; Rigaku Oxford Diffraction, 2021)
Tₘᵢₙ = 0.614, Tₘₐₓ = 1.000
26797 measured reflections
5424 independent reflections
5324 reflections with I > 2σ(I)
R_int = 0.018
θ_max = 76.3°, θ_min = 2.6°
h = −12→15
k = −7→7
l = −42→39

Refinement

Refinement on F²
Least-squares matrix: full
R[F² > 2σ(F²)] = 0.032
wR(F²) = 0.089
S = 1.03
5424 reflections
310 parameters
0 restraints
Primary atom site location: dual
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
w = 1/[σ²(F°²) + (0.0576P)² + 0.4171P]
where P = (F°² + 2Fc²)/3
(Δ/σ)_max = 0.001
Δρ_max = 0.23 e Å⁻³
Δρ_min = −0.14 e Å⁻³
Absolute structure: Flack x determined using 2226 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons et al., 2013)
Absolute structure parameter: −0.07 (4)
**Special details**

**Experimental.** Data collection and full structure determination done by Prof. Anthony Linden: anthony.linden@chem.uzh.ch

Solvent used: dichloromethane / MeOH Cooling Device: Oxford Instruments Cryojet XL Crystall mount: on a cryo-loop

Frames collected: 2026 Seconds exposure per frame: 3.5-14.0 Degrees rotation per frame: 0.8 Crystal-detector distance (mm): 52.0 Client: Placide Toklo Sample code: CCG3 (L2101)

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

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

| Atom | x  | y  | z  | Uiso/σ(Ueq) |
|------|----|----|----|-------------|
| O3   | 0.0614 (2) | 0.56528 (11) | 0.76377 (4) | 0.0366 (3) |
| O20  | 0.68894 (19) | 0.47972 (9) | 0.43024 (3) | 0.0267 (2) |
| O25  | 0.5723 (2) | 0.56885 (11) | 0.33129 (4) | 0.0383 (3) |
| H25  | 0.523 (5) | 0.533 (2) | 0.3098 (9) | 0.064 (8)* |
| C1   | 0.3227 (3) | 0.65364 (12) | 0.67560 (4) | 0.0237 (3) |
| H11  | 0.372968 | 0.724695 | 0.664664 | 0.028* |
| H12  | 0.195700 | 0.631884 | 0.660685 | 0.028* |
| C2   | 0.2636 (3) | 0.67035 (13) | 0.71904 (5) | 0.0272 (3) |
| H21  | 0.383434 | 0.705011 | 0.732882 | 0.033* |
| H22  | 0.143704 | 0.722196 | 0.720494 | 0.033* |
| C3   | 0.2054 (2) | 0.56533 (13) | 0.74025 (4) | 0.0236 (3) |
| C4   | 0.3385 (2) | 0.46238 (13) | 0.73290 (4) | 0.0226 (3) |
| C5   | 0.4116 (2) | 0.45682 (12) | 0.68894 (4) | 0.0188 (3) |
| H5   | 0.281213 | 0.438591 | 0.673871 | 0.023* |
| C6   | 0.5604 (3) | 0.35971 (13) | 0.68050 (4) | 0.0260 (3) |
| H61  | 0.703880 | 0.378314 | 0.689480 | 0.031* |
| H62  | 0.512931 | 0.293418 | 0.695096 | 0.031* |
| C7   | 0.5619 (3) | 0.33575 (12) | 0.63620 (4) | 0.0252 (3) |
| H71  | 0.419165 | 0.313371 | 0.627931 | 0.030* |
| H72  | 0.657416 | 0.272910 | 0.631022 | 0.030* |
| C8   | 0.6320 (2) | 0.43510 (12) | 0.61106 (4) | 0.0185 (3) |
| C9   | 0.5085 (2) | 0.54127 (12) | 0.62390 (4) | 0.0185 (3) |
| H9   | 0.360501 | 0.527212 | 0.615499 | 0.022* |
| C10  | 0.4939 (2) | 0.56510 (12) | 0.66945 (4) | 0.0195 (3) |
| C11  | 0.5794 (3) | 0.64105 (12) | 0.59911 (5) | 0.0294 (4) |
| H11  | 0.500748 | 0.707373 | 0.607671 | 0.035* |
| H112 | 0.730310 | 0.654847 | 0.603899 | 0.035* |
| C12  | 0.5438 (3) | 0.62294 (13) | 0.55480 (5) | 0.0301 (4) |
| H121 | 0.391393 | 0.619297 | 0.549339 | 0.036* |
| H122 | 0.602645 | 0.686024 | 0.539868 | 0.036* |
| C13  | 0.6481 (2) | 0.51636 (12) | 0.54125 (4) | 0.0200 (3) |
| H13  | 0.802446 | 0.525914 | 0.545313 | 0.024* |
| C14  | 0.5806 (2) | 0.41520 (11) | 0.56615 (4) | 0.0180 (3) |
| C15  | 0.7030 (3) | 0.32294 (13) | 0.54484 (4) | 0.0260 (3) |
| Atom  | X        | Y        | Z        | U(eq)  |
|-------|----------|----------|----------|--------|
| H151  | 0.637064 | 0.250069 | 0.549519 | 0.031* |
| H152  | 0.850337 | 0.320332 | 0.554027 | 0.031* |
| C16   | 0.6918 (3)| 0.35461 (12) | 0.50053 (5) | 0.0259 (3) |
| H161  | 0.591387 | 0.306133 | 0.486510 | 0.031* |
| H162  | 0.831463 | 0.346643 | 0.488066 | 0.031* |
| C17   | 0.6177 (2)| 0.47688 (12) | 0.49860 (4) | 0.0210 (3) |
| H17   | 0.463304 | 0.475829 | 0.493403 | 0.025* |
| C18   | 0.8707 (2)| 0.44709 (17) | 0.61720 (5) | 0.0308 (4) |
| H181  | 0.942299 | 0.382284 | 0.606306 | 0.046* |
| H182  | 0.901022 | 0.452861 | 0.645468 | 0.046* |
| H183  | 0.920345 | 0.513756 | 0.603717 | 0.046* |
| C19   | 0.7012 (3)| 0.60844 (15) | 0.68675 (5) | 0.0301 (4) |
| H191  | 0.674285 | 0.643034 | 0.712398 | 0.045* |
| H192  | 0.762195 | 0.663044 | 0.668751 | 0.045* |
| H193  | 0.799351 | 0.546840 | 0.690139 | 0.045* |
| C20   | 0.7195 (3)| 0.54464 (13) | 0.46553 (4) | 0.0235 (3) |
| C21   | 0.9537 (3)| 0.56494 (16) | 0.47150 (5) | 0.0335 (4) |
| H211  | 1.025188 | 0.494256 | 0.475736 | 0.050* |
| H212  | 0.974672 | 0.612534 | 0.494551 | 0.050* |
| H213  | 1.011747 | 0.601056 | 0.448031 | 0.050* |
| C22   | 0.6000 (3)| 0.65290 (14) | 0.45674 (5) | 0.0332 (4) |
| H221  | 0.458482 | 0.651127 | 0.468784 | 0.040* |
| H222  | 0.677386 | 0.717209 | 0.467389 | 0.040* |
| C23   | 0.5841 (5)| 0.66006 (16) | 0.41220 (6) | 0.0493 (6) |
| H231  | 0.663996 | 0.724317 | 0.402167 | 0.059* |
| H232  | 0.435919 | 0.667410 | 0.403866 | 0.059* |
| C24   | 0.6782 (3)| 0.55194 (14) | 0.39679 (5) | 0.0290 (3) |
| H241  | 0.824204 | 0.566913 | 0.387394 | 0.035* |
| C25   | 0.5587 (3)| 0.49359 (14) | 0.36403 (5) | 0.0287 (3) |
| C26   | 0.6673 (5)| 0.38558 (18) | 0.35407 (6) | 0.0534 (6) |
| H261  | 0.599919 | 0.352188 | 0.330977 | 0.080* |
| H262  | 0.656627 | 0.335036 | 0.376565 | 0.080* |
| H263  | 0.815451 | 0.399764 | 0.348232 | 0.080* |
| C27   | 0.3300 (4)| 0.4732 (2) | 0.37400 (8) | 0.0544 (6) |
| H271  | 0.258291 | 0.544080 | 0.377597 | 0.082* |
| H272  | 0.320624 | 0.430056 | 0.398405 | 0.082* |
| H273  | 0.263273 | 0.432252 | 0.352442 | 0.082* |
| C28   | 0.5200 (3)| 0.46709 (16) | 0.76308 (5) | 0.0309 (4) |
| H281  | 0.593564 | 0.537809 | 0.760579 | 0.046* |
| H282  | 0.618130 | 0.406468 | 0.757973 | 0.046* |
| H283  | 0.463258 | 0.459995 | 0.789841 | 0.046* |
| C29   | 0.2025 (3)| 0.36060 (14) | 0.74188 (5) | 0.0319 (4) |
| H291  | 0.158615 | 0.362360 | 0.769587 | 0.048* |
| H292  | 0.284021 | 0.293369 | 0.736939 | 0.048* |
| H293  | 0.078292 | 0.361165 | 0.724853 | 0.048* |
| C30   | 0.3448 (3)| 0.39001 (14) | 0.55941 (5) | 0.0263 (3) |
| H301  | 0.261228 | 0.455077 | 0.566392 | 0.039* |
| H302  | 0.302654 | 0.327509 | 0.575989 | 0.039* |
### Atomic displacement parameters (Å²)

|   | $U^{11}$  | $U^{22}$  | $U^{33}$  | $U^{12}$  | $U^{13}$  | $U^{23}$  |
|---|-----------|-----------|-----------|-----------|-----------|-----------|
| O3| 0.0359 (7) | 0.0451 (7) | 0.0287 (6) | 0.0077 (6) | 0.0136 (5) | 0.0054 (5) |
| O20| 0.0382 (6) | 0.0251 (5) | 0.0169 (5) | 0.0019 (5) | 0.0004 (4) | −0.0011 (4) |
| O25| 0.0547 (8) | 0.0376 (7) | 0.0226 (6) | 0.0011 (6) | −0.0077 (6) | 0.0024 (5) |
| C1| 0.0317 (8) | 0.0195 (6) | 0.0199 (7) | 0.0031 (6) | 0.0060 (6) | −0.0006 (5) |
| C2| 0.0241 (7) | 0.0239 (7) | 0.0234 (7) | 0.0028 (6) | 0.0078 (6) | −0.0038 (6) |
| C3| 0.0247 (7) | 0.0264 (7) | 0.0168 (6) | 0.0006 (6) | 0.0012 (5) | 0.0014 (5) |
| C4| 0.0186 (6) | 0.0201 (6) | 0.0178 (6) | 0.0000 (6) | −0.0001 (5) | −0.0002 (5) |
| C5| 0.0311 (8) | 0.0257 (7) | 0.0211 (7) | 0.0097 (7) | 0.0024 (6) | 0.0030 (6) |
| C7| 0.0347 (8) | 0.0185 (6) | 0.0225 (7) | 0.0059 (6) | 0.0046 (6) | 0.0011 (5) |
| C8| 0.0170 (6) | 0.0196 (6) | 0.0189 (6) | 0.0017 (5) | 0.0028 (5) | −0.0014 (5) |
| C9| 0.0203 (6) | 0.0175 (6) | 0.0176 (6) | −0.0008 (5) | 0.0027 (5) | −0.0021 (5) |
| C10| 0.0196 (7) | 0.0209 (7) | 0.0181 (6) | −0.0015 (5) | 0.0020 (5) | −0.0027 (5) |
| C11| 0.0472 (10) | 0.0175 (7) | 0.0235 (7) | −0.0024 (7) | 0.0129 (7) | −0.0023 (5) |
| C12| 0.0482 (10) | 0.0186 (7) | 0.0234 (7) | 0.0055 (7) | 0.0114 (7) | 0.0017 (6) |
| C13| 0.0224 (7) | 0.0182 (6) | 0.0194 (6) | −0.0010 (5) | 0.0046 (5) | −0.0018 (5) |
| C14| 0.0179 (6) | 0.0157 (6) | 0.0204 (7) | 0.0003 (5) | 0.0031 (5) | −0.0018 (5) |
| C15| 0.0341 (9) | 0.0201 (7) | 0.0237 (7) | 0.0054 (6) | 0.0046 (6) | −0.0030 (5) |
| C16| 0.0328 (8) | 0.0215 (7) | 0.0234 (7) | 0.0005 (6) | 0.0055 (6) | −0.0044 (6) |
| C17| 0.0219 (7) | 0.0219 (7) | 0.0193 (6) | −0.0005 (5) | 0.0030 (6) | −0.0022 (5) |
| C18| 0.0179 (7) | 0.0494 (10) | 0.0250 (7) | 0.0034 (7) | 0.0004 (6) | −0.0054 (7) |
| C19| 0.0262 (8) | 0.0373 (8) | 0.0269 (8) | −0.0104 (7) | 0.0022 (6) | −0.0084 (7) |
| C20| 0.0279 (8) | 0.0245 (7) | 0.0180 (7) | −0.0018 (6) | 0.0032 (6) | −0.0026 (6) |
| C21| 0.0301 (8) | 0.0444 (10) | 0.0260 (8) | −0.0102 (8) | 0.0050 (7) | 0.0010 (7) |
| C22| 0.0457 (10) | 0.0271 (8) | 0.0267 (8) | 0.0041 (7) | 0.0080 (7) | 0.0026 (6) |
| C23| 0.0884 (17) | 0.0286 (9) | 0.0307 (9) | 0.0071 (10) | −0.0128 (11) | −0.0005 (7) |
| C24| 0.0321 (8) | 0.0325 (8) | 0.0222 (7) | −0.0033 (7) | 0.0006 (6) | 0.0030 (6) |
| C25| 0.0342 (9) | 0.0297 (8) | 0.0222 (7) | 0.0034 (7) | −0.0024 (6) | 0.0005 (6) |
| C26| 0.0894 (18) | 0.0405 (10) | 0.0302 (9) | 0.0235 (12) | −0.0139 (11) | −0.0088 (8) |
| C27| 0.0383 (11) | 0.0647 (14) | 0.0602 (13) | −0.0147 (11) | −0.0085 (10) | 0.0096 (11) |
| C28| 0.0330 (8) | 0.0396 (9) | 0.0200 (7) | 0.0043 (7) | −0.0051 (6) | 0.0002 (6) |
| C29| 0.0398 (9) | 0.0293 (8) | 0.0266 (8) | −0.0041 (7) | 0.0085 (7) | 0.0037 (6) |
| C30| 0.0215 (7) | 0.0348 (8) | 0.0226 (7) | −0.0082 (6) | 0.0015 (6) | −0.0029 (6) |

### Geometric parameters (Å, °)

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| O3—C3| 1.216 (2) | C15—H151| 0.9900 |
| O20—C24| 1.4334 (19) | C15—H152| 0.9900 |
| O20—C20| 1.4446 (17) | C16—C17| 1.555 (2) |
| O25—C25| 1.439 (2) | C16—H161| 0.9900 |
| O25—H25| 0.90 (3) | C16—H162| 0.9900 |
| C1—C2| 1.533 (2) | C17—C20| 1.533 (2) |
| C1—C10| 1.544 (2) | C17—H17| 1.0000 |

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| Bond          | Length (Å) | Bond          | Length (Å) |
|--------------|------------|--------------|------------|
| C1—H11       | 0.9900     | C18—H181     | 0.9800     |
| C1—H12       | 0.9900     | C18—H182     | 0.9800     |
| C2—C3        | 1.507 (2)  | C18—H183     | 0.9800     |
| C2—H21       | 0.9900     | C19—H191     | 0.9800     |
| C2—H22       | 0.9900     | C19—H192     | 0.9800     |
| C3—C4        | 1.528 (2)  | C19—H193     | 0.9800     |
| C4—C29       | 1.537 (2)  | C20—C21      | 1.527 (2)  |
| C4—C28       | 1.545 (2)  | C20—C22      | 1.545 (2)  |
| C4—C5        | 1.5627 (19)| C21—H211     | 0.9800     |
| C5—C6        | 1.537 (2)  | C21—H212     | 0.9800     |
| C5—C10       | 1.5589 (19)| C21—H213     | 0.9800     |
| C5—H5        | 1.0000     | C22—C23      | 1.515 (2)  |
| C6—C7        | 1.529 (2)  | C22—H221     | 0.9900     |
| C6—H61       | 0.9900     | C22—H222     | 0.9900     |
| C6—H62       | 0.9900     | C23—C24      | 1.532 (3)  |
| C7—C8        | 1.540 (2)  | C23—H231     | 0.9900     |
| C7—H71       | 0.9900     | C23—H232     | 0.9900     |
| C7—H72       | 0.9900     | C24—C25      | 1.520 (2)  |
| C8—C18       | 1.542 (2)  | C24—H241     | 1.0000     |
| C8—C9        | 1.5691 (19)| C25—C27      | 1.517 (3)  |
| C8—C14       | 1.5756 (19)| C25—C26      | 1.518 (3)  |
| C9—C11       | 1.539 (2)  | C26—H261     | 0.9800     |
| C9—C10       | 1.5731 (18)| C26—H262     | 0.9800     |
| C9—H9        | 1.0000     | C26—H263     | 0.9800     |
| C10—C19      | 1.538 (2)  | C27—H271     | 0.9800     |
| C11—C12      | 1.534 (2)  | C27—H272     | 0.9800     |
| C11—H111     | 0.9900     | C27—H273     | 0.9800     |
| C11—H112     | 0.9900     | C28—H281     | 0.9800     |
| C12—C13      | 1.523 (2)  | C28—H282     | 0.9800     |
| C12—H121     | 0.9900     | C28—H283     | 0.9800     |
| C12—H122     | 0.9900     | C29—H291     | 0.9800     |
| C13—C17      | 1.5346 (19)| C29—H292     | 0.9800     |
| C13—C14      | 1.5484 (19)| C29—H293     | 0.9800     |
| C13—H13      | 1.0000     | C30—H301     | 0.9800     |
| C14—C15      | 1.5421 (19)| C30—H302     | 0.9800     |
| C14—C30      | 1.550 (2)  | C30—H303     | 0.9800     |
| C15—C16      | 1.551 (2)  |              |            |
| C24—O20—C20  | 109.23 (12)| C15—C16—H161| 110.4      |
| C25—O25—H25  | 107.1 (19) | C17—C16—H161| 110.4      |
| C2—C1—C10    | 113.27 (13)| C15—C16—H162| 110.4      |
| C2—C1—H11    | 108.9      | C17—C16—H162| 110.4      |
| C10—C1—H11   | 108.9      | H161—C16—H162| 108.6     |
| C2—C1—H12    | 108.9      | C20—C17—C13  | 117.94 (12)|
| C10—C1—H12   | 108.9      | C20—C17—C16  | 114.31 (12)|
| H11—C1—H12   | 107.7      | C13—C17—C16  | 102.63 (12)|
| C3—C2—C1     | 114.03 (13)| C20—C17—H17  | 107.1      |
| C3—C2—H21    | 108.7      | C13—C17—H17  | 107.1      |
| Bond               | Angle (°) | Bond               | Angle (°) | Bond               | Angle (°) |
|--------------------|-----------|--------------------|-----------|--------------------|-----------|
| C1—C2—H21         | 108.7     | C16—C17—H17       | 107.1     |
| C3—C2—H22         | 108.7     | C8—C18—H181       | 109.5     |
| C1—C2—H22         | 108.7     | C8—C18—H182       | 109.5     |
| H21—C2—H22        | 107.6     | H181—C18—H182     | 109.5     |
| O3—C3—C2          | 119.93 (15)| C8—C18—H183      | 109.5     |
| O3—C3—C4          | 121.69 (15)| H181—C18—H183    | 109.5     |
| C2—C3—C4          | 118.30 (13)| H182—C18—H183    | 109.5     |
| C3—C4—C29         | 107.99 (13)| C10—C19—H191     | 109.5     |
| C3—C4—C28         | 106.12 (13)| C10—C19—H192     | 109.5     |
| C29—C4—C28        | 108.70 (13)| H191—C19—H192    | 109.5     |
| C3—C4—C5          | 110.85 (12)| C10—C19—H193     | 109.5     |
| C29—C4—C5         | 108.81 (12)| H191—C19—H193    | 109.5     |
| C28—C4—C5         | 114.18 (13)| H192—C19—H193    | 109.5     |
| C6—C5—C10         | 110.90 (12)| O20—C20—C21      | 109.20 (13)|
| C6—C5—C4          | 113.21 (12)| O20—C20—C17      | 104.91 (12)|
| C10—C5—C4         | 117.92 (12)| C21—C20—C17      | 113.77 (13)|
| C6—C5—H5          | 104.4     | O20—C20—C22      | 103.63 (12)|
| C10—C5—H5         | 104.4     | C21—C20—C22      | 111.79 (15)|
| C4—C5—H5          | 104.4     | C17—C20—C22      | 112.74 (13)|
| C7—C6—C5          | 109.37 (12)| C20—C21—H211    | 109.5     |
| C7—C6—H61         | 109.8     | C20—C21—H212     | 109.5     |
| C5—C6—H61         | 109.8     | H211—C21—H212    | 109.5     |
| C7—C6—H62         | 109.8     | C20—C21—H213     | 109.5     |
| C5—C6—H62         | 109.8     | H211—C21—H213    | 109.5     |
| H61—C6—H62        | 108.2     | H212—C21—H213    | 109.5     |
| C6—C7—C8          | 113.39 (13)| C23—C22—C20      | 105.87 (14)|
| C6—C7—H71         | 108.9     | C23—C22—H221     | 110.6     |
| C8—C7—H71         | 108.9     | C20—C22—H221     | 110.6     |
| C6—C7—H72         | 108.9     | C23—C22—H222     | 110.6     |
| C8—C7—H72         | 108.9     | C20—C22—H222     | 110.6     |
| H71—C7—H72        | 107.7     | H221—C22—H222    | 108.7     |
| C7—C8—C18         | 106.56 (13)| C22—C23—C24      | 105.36 (15)|
| C7—C8—C9          | 109.92 (11)| C22—C23—H231     | 110.7     |
| C18—C8—C9         | 112.36 (12)| C24—C23—H231     | 110.7     |
| C7—C8—C14         | 110.77 (12)| C22—C23—H232     | 110.7     |
| C18—C8—C14        | 110.49 (12)| C24—C23—H232     | 110.7     |
| C9—C8—C14         | 106.79 (11)| H231—C23—H232    | 108.8     |
| C11—C9—C8         | 110.13 (11)| O20—C24—C25      | 108.54 (13)|
| C11—C9—C10        | 114.16 (12)| O20—C24—C23      | 105.68 (13)|
| C8—C9—C10         | 116.89 (11)| C25—C24—C23      | 116.75 (16)|
| C11—C9—H9         | 104.8     | O20—C24—H241     | 108.5     |
| C8—C9—H9          | 104.8     | C25—C24—H241     | 108.5     |
| C10—C9—H9         | 104.8     | C23—C24—H241     | 108.5     |
| C19—C10—C1        | 108.60 (13)| O25—C25—C27      | 109.45 (16)|
| C9—C10—C5         | 110.77 (12)| C25—C25—C26      | 110.28 (15)|
| C10—C10—C9        | 112.69 (12)| C27—C25—C26      | 110.3 (2)  |
| C1—C10—C9         | 107.56 (11)| O25—C25—C24      | 103.81 (14)|
| C1—C10—C9         | 107.56 (11)| C27—C25—C24      | 113.24 (16)|
C5—C10—C9 106.35 (11)  C26—C25—C24 109.54 (15)
C12—C11—C9 112.27 (13)  C25—C26—H261 109.5
C12—C11—H111 109.2  C25—C26—H262 109.5
C9—C11—H111 109.2  H261—C26—H262 109.5
C9—C11—H112 109.2  C26—C25—H261 109.5
H111—C11—H112 107.9  C26—C25—H262 109.5
C13—C12—C11 110.60 (14)  C25—C27—H271 109.5
C13—C12—H121 109.5  C25—C27—H272 109.5
C11—C12—H121 109.5  H271—C27—H272 109.5
C13—C12—H122 109.5  C25—C27—H273 109.5
C11—C12—H122 109.5  H271—C27—H273 109.5
H121—C12—H122 108.1  H272—C27—H273 109.5
C12—C13—C17 119.54 (13)  C4—C28—H281 109.5
C12—C13—C14 112.62 (12)  C4—C28—H282 109.5
C17—C13—C14 103.40 (11)  H281—C28—H282 109.5
C12—C13—H13 106.9  C4—C28—H283 109.5
C17—C13—H13 106.9  H281—C28—H283 109.5
C14—C13—H13 106.9  C4—C28—H283 109.5
C15—C14—C13 100.20 (11)  C4—C29—H291 109.5
C15—C14—C30 106.20 (12)  C4—C29—H292 109.5
C13—C14—C30 111.17 (12)  H291—C29—H292 109.5
C15—C14—C8 117.25 (12)  C4—C29—H293 109.5
C13—C14—C8 110.34 (11)  H291—C29—H293 109.5
C30—C14—C8 111.97 (12)  C4—C29—H293 109.5
C14—C15—C16 104.54 (12)  C4—C30—H301 109.5
C14—C15—H151 110.8  C14—C30—H302 109.5
C16—C15—H151 110.8  C14—C30—H303 109.5
C14—C15—H152 110.8  H301—C30—H302 109.5
C16—C15—H152 110.8  C14—C30—H303 109.5
H151—C15—H152 108.9  H301—C30—H302 109.5
C15—C16—C17 106.85 (12)

C10—C1—C2—C3 −52.7 (2)  C17—C13—C14—C15 47.73 (14)
C1—C2—C3—O3 −140.65 (16)  C12—C13—C14—C30 66.56 (17)
C1—C2—C3—C4 42.4 (2)  C17—C13—C14—C30 −63.86 (14)
O3—C3—C4—C9 27.4 (2)  C12—C13—C14—C8 −57.59 (17)
C2—C3—C4—C9 −155.70 (14)  C17—C13—C14—C8 171.99 (11)
O3—C3—C4—C28 −88.97 (19)  C7—C8—C14—C15 −67.19 (16)
C2—C3—C4—C28 87.89 (17)  C18—C8—C14—C15 50.65 (18)
O3—C3—C4—C5 146.54 (15)  C9—C8—C14—C15 173.12 (12)
C2—C3—C4—C5 −36.60 (19)  C7—C8—C14—C13 179.01 (12)
C3—C4—C5—C6 175.52 (13)  C18—C8—C14—C13 −63.14 (16)
C29—C4—C5—C6 −65.86 (16)  C9—C8—C14—C13 59.34 (14)
C28—C4—C5—C6 55.75 (18)  C7—C8—C14—C30 55.91 (16)
C3—C4—C5—C10 43.72 (17)  C18—C8—C14—C30 173.76 (13)
C29—C4—C5—C10 162.33 (13)  C9—C8—C14—C30 −63.76 (15)
C28—C4—C5—C10 −76.06 (17)  C13—C14—C15—C16 −37.61 (15)
### Hydrogen-bond geometry (Å, °)

| D—H···A | D—H   | H···A   | D···A     | D—H···A |
|---------|-------|--------|-----------|---------|
| O25—H25···O3 | 0.90 (3) | 2.03 (3) | 2.9325 (18) | 172 (3) |

Symmetry code: (i) −x+1/2, −y+1, z−1/2.