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12-Methoxy-15-(4-morpholino)podocarpa-8,11,13-trien-15-one

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Key indicators

Single-crystal X-ray study
T = 93 K
Mean σ(C–C) = 0.003 Å
R factor = 0.042
wR factor = 0.111
Data-to-parameter ratio = 11.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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The title compound [systematic name: (6-methoxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)-morpholin-4-yl-methanone], $C_{22}H_{31}NO_3$, was synthesized from natural podocarpic acid *via* amidation of the acid chloride derivative. The crystal structure shows that the morpholino ring adopts a full chair conformation, while the amide N—C bond has partial double-bond character.

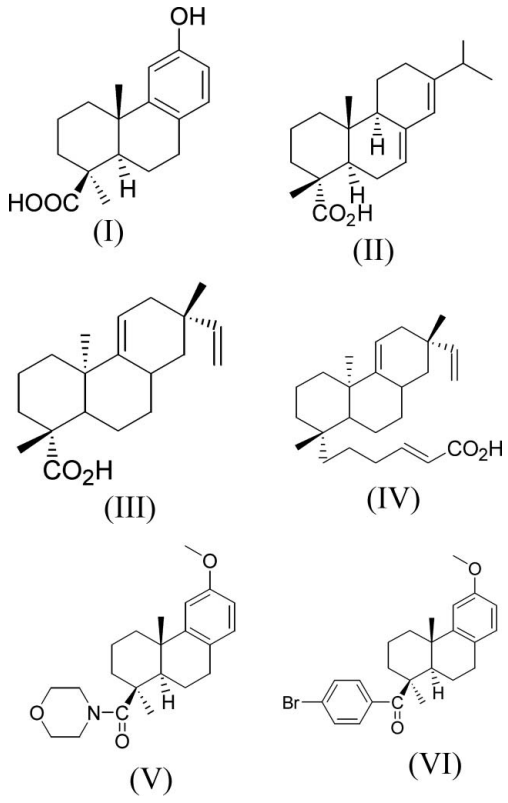
Comment

Podocarpic acid, (I), possesses the ring system common to most tricyclic diterpenoids and it is an attractive scaffold for conversion to compounds with interesting biological activities. Recently, some podocarpic acid analogs have been reported as cytokine release inhibitors and this has consequently led to the discovery of novel anti-inflammatory drugs (He *et al.*, 1999). Other compounds, including a podocarpic acid anhydride, have been shown to be liver *X* receptor α and β agonists. These two nuclear oxysterol receptors in the liver are involved in cholesterol and lipid metabolism. Thus, any of their agonists could be useful in the development of drugs for the treatment of atherosclerosis (Singh *et al.*, 2005). Structurally related abietic acid, (II), and acanthoic acid, (III), derivatives have been shown to possess lipoxygenase (Ulusu *et al.*, 2002) and cyclooxygenase-2 (COX-2; Suh *et al.*, 2001) inhibitory activities, respectively. Derivatization of the C-4 carboxyl group of acanthoic acid to form an elongated fatty acid chain, (IV), was found significantly to enhance its COX-2 inhibitory activity as well as its selectivity (Suh *et al.*, 2001). These compounds were subsequently shown to possess excellent anti-inflammatory activities (Suh *et al.*, 2004). In addition, some newly isolated abietane diterpenes were recently reported to possess strong inhibitory activities on certain colon, lung and breast human tumors (Son *et al.*, 2005).

As part of our anti-inflammatory and anticancer discovery program, we are exploring the derivatization of the C-4 carboxyl group of podocarpic acid in order to design new molecules that can modulate the lipoxygenase and cyclooxygenase pathways. Consequently, the title morpholino derivative, (V), was synthesized as one of a series of amide derivatives under investigation. In order to establish a database of structural data for such compounds, the X-ray structural analysis of (V) was undertaken and the results are presented here.

Selected bond distances and angles for (V) are listed in Table 1. The overall molecular geometry, with the atom-numbering scheme, is illustrated in Fig. 1. Since this compound was synthesized from natural podocarpic acid and the stereocenters were intact during the reactions, the stereochemistry of the compound is as shown. As expected, ring *A*

adopts the usual chair conformation, as previously reported (Mondal *et al.*, 2003; Couldwell *et al.*, 1985), while ring *B* is observed in the half-chair conformation as a result of being fused to the planar aromatic ring *C*. The methoxy substituent at C12 is displaced from the plane of aromatic ring *C* by 0.376 (4) Å. Comparison with 19-(*p*-bromophenyl)-12-methoxypodocarpa-8,11,13-trien-19-one, (VI) (Couldwell *et al.*, 1985), indicates that some bonds are longer than in the



morpholino amide derivative (V), but the differences are very small, perhaps barely significant. For example, the O2—C12 bond at 1.374 (3) Å is insignificantly longer than the previously reported value of 1.363 (9) Å for compound (VI), while the O2—C18 bond is 1.431 (3) Å, compared with 1.39 (1) Å in (VI). The carbonyl functionality has a C=O bond length of 1.236 (2) Å in the amide, compared with 1.225 (7) Å in the ketone, which agrees with standard average values for these bond types (Allen, 1980). The N—C15 bond length is 1.369 (3) Å, indicating partial double-bond character and thus signifying a typical conjugation of the lone pair of electrons on the morpholino N atom with the π electrons of the C=O double bond of the carbonyl group. However, the amide section (C19/C22/N/C15/O1) is not quite planar. Perhaps due to intramolecular crowding (the H3*A*···H19*A* distance is only 1.83 Å), atom C19 is slightly out of the plane, as indicated by the deviation of the two torsion angles, C19—N—C15—O1 = 157.5 (2)° and C19—N—C15—C4 = −23.1 (3)°, from planar values. The morpholino ring, however, adopts a full-chair conformation.

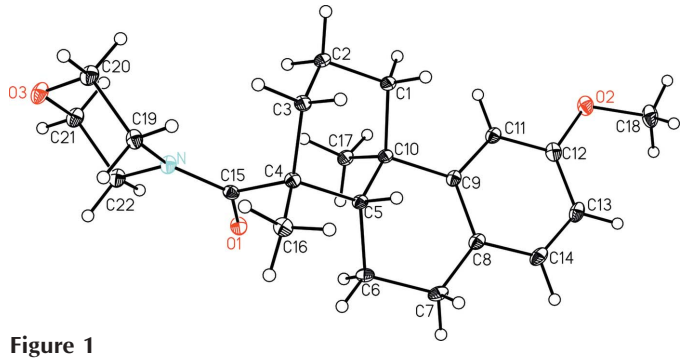


Figure 1
A view of the molecule of (V), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 20% probability level and H atoms are shown as circles of arbitrary size.

Experimental

A solution of 12-methoxypodocarpic acid (0.5375 g, 1.864 mmol) in dry benzene (13 ml) was added dropwise to dry sodium hydride (100 mg). The resulting suspension was stirred for 30 min, after which oxalyl chloride (2 ml) was carefully added and the reaction mixture was stirred at room temperature for 1 h. The mixture was then filtered and the solvent evaporated. The resulting residue was dissolved in dry benzene (5 ml) and added dropwise to a stirred solution (273 K) of morpholine in dry benzene (10 ml). After stirring at room temperature for 24 h, the reaction mixture was diluted with dichloromethane, filtered, and the filtrate concentrated *in vacuo*. Treatment of the residue with hexane gave a white amorphous solid, which was crystallized from aqueous ethanol to furnish the title amide, (V) (0.644 g, 96%). Apart from the X-ray crystallographic analysis presented in this paper, the product, (V), was characterized by FT–IR spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopies, and GCMS in order to obtain mass spectroscopic data. All the data obtained confirmed the structure of (V).

Crystal data

$C_{22}H_{31}NO_3$
M_r = 357.48
Orthorhombic, $P2_12_12_1$
a = 14.4202 (14) Å
b = 7.1619 (7) Å
c = 18.5166 (18) Å
V = 1912.3 (3) Å^3
Z = 4
D_x = 1.242 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 6672 reflections
θ = 2.6–28.2°
μ = 0.08 mm^{-1}
T = 93 (2) K
Chunk, colorless
0.56 × 0.45 × 0.35 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1997)
T_{min} = 0.759, T_{max} = 1.000
14733 measured reflections
2650 independent reflections
2340 reflections with $I > 2\sigma(I)$
R_{int} = 0.064
θ_{max} = 28.4°
$h = -19 \rightarrow 19$
$k = -9 \rightarrow 8$
$l = -24 \rightarrow 24$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.111
S = 1.04
2650 reflections
238 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.06P)^2 + 0.669P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

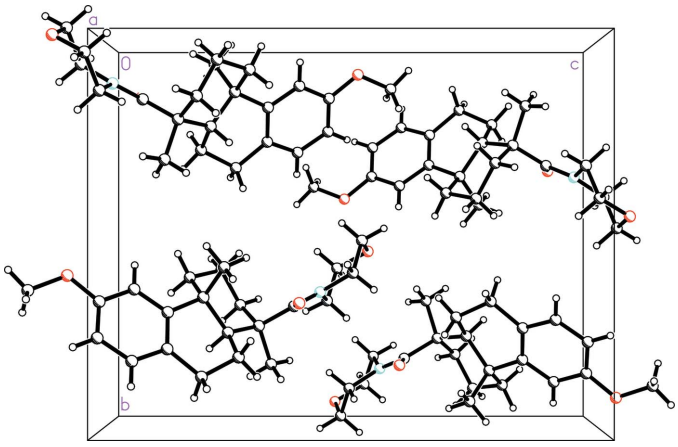


Figure 2
The molecular packing of (V), viewed along the *a* axis.

Table 1
Selected geometric parameters (Å, °).

O1—C15	1.236 (2)	C2—C3	1.508 (3)
O2—C12	1.374 (3)	C3—C4	1.540 (3)
O2—C18	1.429 (3)	C4—C15	1.541 (3)
O3—C20	1.423 (3)	C4—C16	1.555 (3)
O3—C21	1.427 (3)	C4—C5	1.566 (3)
N—C15	1.370 (3)	C5—C6	1.541 (3)
N—C22	1.471 (3)	C5—C10	1.560 (3)
N—C19	1.474 (3)	C10—C17	1.540 (3)
C1—C2	1.524 (3)	C19—C20	1.512 (3)
C1—C10	1.552 (3)	C21—C22	1.510 (3)
C12—O2—C18	116.6 (2)	O2—C12—C13	124.6 (2)
C20—O3—C21	109.76 (18)	O1—C15—N	118.5 (2)
C15—N—C22	117.83 (17)	O1—C15—C4	119.67 (19)
C15—N—C19	129.19 (19)	N—C15—C4	121.80 (17)
C22—N—C19	110.04 (18)	N—C19—C20	109.65 (19)
C15—C4—C16	107.60 (17)	N—C19—H19*A*	110
C3—C4—C5	106.30 (16)	O3—C20—C19	111.39 (19)
C15—C4—C5	112.04 (16)	O3—C21—C22	111.7 (2)
C16—C4—C5	107.78 (18)	N—C22—C21	110.04 (19)
O2—C12—C11	115.2 (2)		

All H atoms were initially located in a difference Fourier map. The methyl H atoms were then constrained to an ideal geometry, with C—H distances of 0.98 Å and $U_{iso}(H) = 1.5U_{eq}(C)$, but each group was allowed to rotate freely about its C—C bond. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C—H distances in the range 0.95–1.00 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$. In the absence of significant anomalous scattering effects, Friedel pairs were merged.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997*a*); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997*a*); molecular graphics: *SHELXTL* (Sheldrick, 1997*b*); software used to prepare material for publication: *SHELXTL*.

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