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3,3-Dichloro-1-(*p*-chlorophenyl)-4-(*p*-methoxyphenyl)-2-azetidinone

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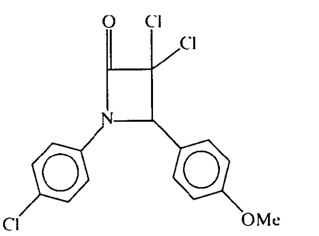
Abstract

The crystal structure of the title compound, $C_{16}H_{12}Cl_3NO_2$, has a nearly planar β-lactam ring with the N atom out of the best plane by 0.032 (2) Å. The C—C bond distances in the β-lactam ring are 1.544 (4) and 1.568 (4) Å. The chlorophenyl and methoxyphenyl rings are nearly perpendicular to one another [81.92 (7)°].

Comment

The β-lactam ring (2-azetidinone) plays a key role in the most widely employed class of antimicrobial agents. The activity and selectivity of the β-lactam ring can be influenced decisively by the attached substituent (Kumar *et al.*, 1993; Sharma *et al.*, 1994; Manhas *et al.*, 1988). Since to determine antibacterial activity a complete knowledge of the stereochemistry of the β-lactam ring is required, an X-ray analysis of the title compound, 3,3-dichloro-1-(*p*-chlorophenyl)-4-(*p*-methoxyphenyl)-2-azetidinone, (I), was performed. Previously, some structural studies were carried out on similar compound obtained by changing the substituents on the β-lactam ring (Ercan *et al.*, 1996*a,b*; Ülkü *et al.*, 1997; Kabak *et al.*, 1999).



(I)

The four-membered β-lactam ring of (I) is nearly planar, with a slight deviation of the N1 atom from the best plane [0.032 (2) Å]. The bond lengths in the lactam ring are comparable with those in monocyclic 2-azetidinones (Ercan *et al.*, 1996*a,b*, and references therein). Due to the different substituents attached to the β-lactam ring, the C7—C8 and C8—C9 bond distances differ slightly from those of previous works (Table 2). The bond angle C7—C8—C9 (tetrahedral configuration maintained by C8) is 85.9 (2)° and is nearly equal to the angles in previous studies (Ercan *et al.*, 1996*a,b*; Ülkü *et al.*, 1997; Kabak *et al.*, 1999).

The dihedral angle between the chlorophenyl and methoxyphenyl rings shows that the two substituents are nearly perpendicular to one another [81.92 (7)°]; the corresponding torsion angle C6—N1—C9—C10 is −67.2 (3)°. The β-lactam ring is coplanar with the chlorophenyl substituent [dihedral angle 9.7 (2)°], while the corresponding angle with the methoxyphenyl ring is 72.2 (1)°.

Brufani & Cella (1984) suggested that the antibiotic activity of the β-lactam series may depend on the geometrical features of the β-lactam structures (such as the deviation of the N1 atom from the surrounding atoms and the sum of the bond angles at the N1 atom). They concluded that when the N1 atom deviates by 0.4–0.5 Å from the plane containing the other peripheral C7, C6 and C9 atoms, the β-lactam structure could have antibiotic activity. In the present case, the amide N atom in the β-lactam ring is 0.108 (4) Å above the plane containing the C7, C6 and C9 atoms. Due to the substituents present in (I), the deviation of the N1 atom from the C7/C6/C9 plane is larger than in the other structures listed in Table 2. The sum of the bond angles at the N1 atom is 360°, which shows the planar array in (I). Thus, according to the conclusion of Brufani & Cella (1984), the title compound should be inactive.

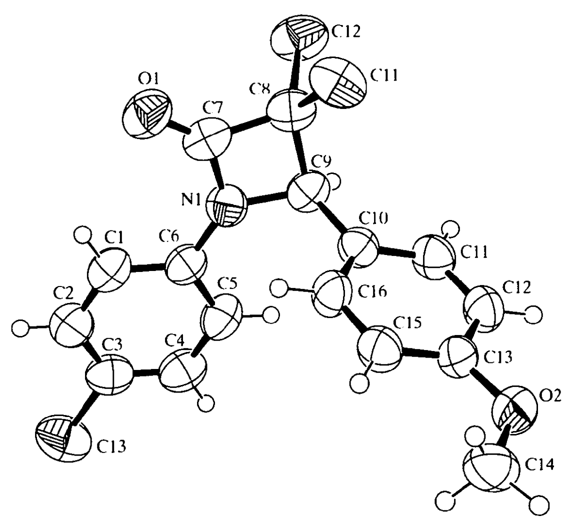


Fig. 1. *ORTEP*-3 (Farrugia, 1997) drawing of the title molecule with the atom-numbering sheme. Displacement ellipsoids are shown at the 50% probability level.

In the title molecule, there are no considerable intermolecular and intramolecular interactions between molecules or atoms.

Experimental

N-p-Methoxybenzylidene-*p*-chloroaniline (2.295 g, 0.01 mol) and triethylamine (2.78 ml, 0.02 mol) in benzene (50 ml) were stirred for 15 min. Dichloroacetyl chloride (2.78 ml, 0.02 mol) was added dropwise to the solution and the mixture was stirred at room temperature for 1 h. The triethylamine salts were filtered off and the product was recrystallized from ethanol.

Crystal data

$C_{16}H_{12}Cl_3NO_2$
$M_r = 356.62$
Monoclinic
$P2_1/n$
$a = 5.865 (2)$ Å
$b = 14.179 (3)$ Å
$c = 19.487 (3)$ Å
$\beta = 94.33 (4)°$
$V = 1615.7 (7)$ Å^3
$Z = 4$
$D_x = 1.466$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.7107$ Å
Cell parameters from 25 reflections
$\theta = 3.7–7.6°$
$\mu = 0.572$ mm^{-1}
$T = 295.2$ K
Prismatic
0.80 × 0.35 × 0.30 mm
Colorless

Data collection

Rigaku AFC-7*S* diffractometer
$\omega–2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.782$, $T_{max} = 0.842$
3862 measured reflections
3862 independent reflections

2045 reflections with $I > 2\sigma(I)$
$\theta_{max} = 28.53°$
$h = 0 \rightarrow 7$
$k = 0 \rightarrow 19$
$l = -26 \rightarrow 26$
3 standard reflections every 150 reflections intensity decay: −5.34%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.065$
$wR(F^2) = 0.206$
$S = 1.227$
3861 reflections
197 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max} = 0.428$ e Å^{-3}
$\Delta\rho_{min} = -0.323$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Cl1—C8	1.760 (3)	N1—C7	1.370 (3)
Cl2—C8	1.755 (3)	N1—C6	1.398 (3)
Cl3—C3	1.738 (3)	N1—C9	1.474 (3)
O1—C7	1.193 (3)	C7—C8	1.544 (4)
O2—C13	1.359 (3)	C8—C9	1.568 (4)
O2—C14	1.418 (3)	C9—C10	1.497 (4)
C13—O2—C14	117.5 (2)	C9—C8—Cl2	113.73 (17)
C7—N1—C6	133.9 (2)	C7—C8—Cl1	114.98 (17)
C7—N1—C9	96.4 (2)	C9—C8—Cl1	118.01 (19)
C6—N1—C9	129.7 (2)	Cl2—C8—Cl1	110.48 (15)
C7—C8—C9	85.9 (2)	O2—C13—C15	125.1 (2)
C7—C8—Cl2	111.74 (19)	O2—C13—C12	115.0 (2)

Table 2. *Bond lengths and the deviation (h) of the N1 atom from the C6/C7/C9 plane (Å) compared with previous works*

	Cl—C8	O1—C7	N1—C6	N1—C7
(I)	1.760 (3)	1.213 (4)	1.403 (4)	1.357 (4)
(II)	1.764 (9)	1.188	1.400	1.374
(IV)	1.758 (2)	1.186 (6)	1.417 (5)	1.362 (6)
(V)	1.758 (3)	1.193 (3)	1.398 (3)	1.370 (3)
	N1—C9	C—C8	C9—C10	*h*
(I)	1.482 (4)	1.55 (1)	1.487 (4)	0.031 (1)
(II)	1.467	1.56 (1)	1.470	0.001 (8)
(IV)	1.469 (5)	1.56 (1)	1.505 (6)	0.016 (5)
(V)	1.474 (4)	1.56 (1)	1.497 (4)	0.108 (4)

Notes: (I) 3,3-dichloro-4-(*p*-methoxyphenyl)-1-phenyl-2-azetidinone (Ercan *et al.*, 1996*a*); (II) 3,3-dichloro-1-(*p*-chlorophenyl)-4-phenyl-2-azetidinone (Ercan *et al.*, 1996*b*); (IV) 3,3-dichloro-1,4-diphenyl-2-azetidinone (Kabak *et al.*, (1999); (V) 3,3-dichloro-1-(*p*-chlorophenyl)-4-(*p*-methoxyphenyl)-2-azetidinone (the present work).

All H atoms were placed geometrically on their parent C atoms and refined as riding, except for H9, which was located from a difference Fourier map and refined isotropically.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1994). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN for Windows* (Molecular Structure Corporation, 1997). Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993) and expanded with *DIRDIF*94 (Beurskens *et al.*, 1994). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *ORTEP*-3 (Farrugia, 1997).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: KA1334). Services for accessing these data are described at the back of the journal.

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Five analogs of the active metabolite of leflunomide

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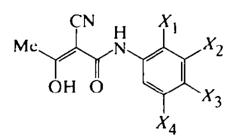
Abstract

The title compounds, 2-cyano-3-hydroxy-*N*-(4-bromophenyl)but-2-enamide, $C_{11}H_9BrN_2O_2$ (LFM-A1), 2-cyano-3-hydroxy-*N*-(2-fluorophenyl)but-2-enamide, $C_{11}H_9FN_2O_2$ (LFM-A7), 2-cyano-3-hydroxy-*N*-(3-bromophenyl)but-2-enamide, $C_{11}H_9BrN_2O_2$ (LFM-A9), 2-cyano-3-hydroxy-*N*-(3-chlorophenyl)but-2-enamide, $C_{11}H_9ClN_2O_2$ (LFM-A10), and 2-cyano-3-hydroxy-*N*-(3-fluorophenyl)but-2-enamide, $C_{11}H_9FN_2O_2$ (LFM-A11), are analogs of A77 1726, the active metabolite of the immunosupressive drug leflunomide, which is known to act in part by inhibiting the tyrosine kinase epidermal growth factor receptor (EGFR) [Mattar, Kochhar, Bartlett, Bremer & Finnegan (1993). *FEBS Lett.* **334**, 161–164]. The molecular structures of the title compounds are very similar and they display similar crystal packing and hydrogen-bonding networks. All five molecules are approximately planar; the dihedral angles between the phenyl ring and the plane defined by the N—C—C=C—CH_3 group are 4.8 (8)° for LFM-A1, 12.5 (2)° for LFM-A7, 6.2 (6)° for LFM-A9, 5.5 (3)° for LFM-A10 and 4.4 (3)° for LFM-A11. The intramolecular hydrogen bond between the O atoms observed in all the compounds locks them into a planar conformation and may contribute to a conformation which is favorable for binding the shallow ATP-binding pocket of EGFR.

† Member of the Drug Discovery Program.

Comment

The epidermal growth factor receptor (EGFR) is a membrane-associated tyrosine kinase which serves as an endogenous negative regulator of apoptosis in breast-cancer cells (Uckun *et al.*, 1998). Consequently, the development of new potent anti-breast-cancer drugs has emerged as an exceptional focal point for translational research in the treatment of breast cancer (Abrams *et al.*, 1994). A77 1726 is the primary metabolite of the isoxazole leflunomide [*N*-(4-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide] and is an anti-inflammatory agent with pleiotropic effects (Parnham, 1995; Xu *et al.*, 1995, 1996; Bertolini *et al.*, 1997). A77 1726 was recently shown to inhibit the EGFR kinase at micromolar concentrations (Mattar *et al.*, 1993). In a systematic effort to design potent inhibitors of this receptor family protein tyrosine kinase (PTK) as anti-breast cancer agents, we have constructed a three-dimensional homology model of the EGFR kinase domain and used advanced docking procedures for the rational placement of chemical groups with defined sizes at multiple modification sites on A77 1726 (LFM) (Ghosh *et al.*, 1998). Based on the modeling studies, A77 1726, along with some of its designed analogs, were synthesized and tested for their kinase inhibitory activity on EGFR. This study is the first report of the structural characterization of five such LFM analogs which target the EGFR tyrosine kinase.



LFM-A1 : $X_1 = X_2 = X_4 =$ H, $X_3 =$ Br
LFM-A7 : $X_2 = X_3 = X_4 =$ H, $X_1 =$ F
LFM-A9 : $X_1 = X_3 = X_4 =$ H, $X_2 =$ Br
LFM-A10 : $X_1 = X_3 = X_4 =$ H, $X_2 =$ Cl
LFM-A11 : $X_1 = X_2 = X_3 =$ H, $X_4 =$ F

The atom numbering scheme and molecular conformation adopted by the molecules are shown in Figs. 1–5. The molecular structures of the title compounds are very similar and they display similar crystal packing and hydrogen-bonding networks. All five structures are approximately planar and there is no significant difference in the corresponding bond distances and angles in the five structures. All bond lengths except the C8—C11 and C11≡N11 bonds are consistent with values for similar types of bonds reported in the Cambridge

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