X-Ray Crystal Structure of a Ligand at the Thromboxane A_2/Prostaglandin H_2 Receptor Site: (4*Z*)-6-[(2*RS*,4*RS*,5*SR*)-2-(2-Chlorophenyl)-4-(2-hydroxyphenyl)-1,3-dioxan-5-yl]hex-4-enoic Acid

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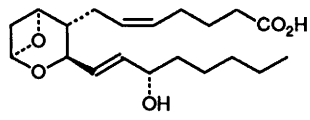
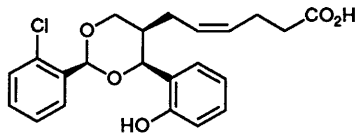
The X-ray crystal structure of a 1,3-dioxane thromboxane receptor antagonist (**2**) is reported, which shows the presence of both an inter- and an intra-molecular hydrogen bond in the molecule and unexpectedly reveals that the hexenoic acid side chain carboxy group lies over the plane of the 1,3-dioxane ring.

Abnormal levels of the arachidonic acid metabolite thromboxane A_2 (**1**; TxA_2) have been implicated in the pathogenesis of a number of human diseases.[1] In order to test for this involvement of TxA_2 (**1**), stable synthetic analogues of TxA_2 and antagonists of its action at the thromboxane A_2/prostaglandin H_2 receptor site, are required. A number of such

compounds have been synthesized[2] including the one based on 1,3-dioxane (2).



(1)



(2)

The design of improved antagonists might be assisted if detailed conformational information for a TxA_2 receptor ligand were available, for example to provide a low-energy conformation for computer graphic modelling studies. We here report the first X-ray crystal structure of such a ligand, the TxA_2 receptor antagonist[3] (4Z)-(6-[(2*RS*,4*RS*,5*SR*)-2-(2-chlorophenyl)-4-(2-hydroxyphenyl)-1,3-dioxan-5-yl]hex-4-enoic acid (2).

Single colourless crystals (m.p. 126–128 °C) of the 1,3-dioxane (2) which were suitable for diffraction were grown from ethyl acetate solutions at 25 °C. Crystal data was collected on a Philips PW 1100 diffractometer using graphite crystal monochromated Mo-K_α radiation.†

The structural analysis confirmed that the 1,3-dioxane ring has an almost perfect chair conformation with the two phenyl rings in equatorial positions (Figure 1). The effect of ring substituents on the conformation of the 1,3-dioxanes has been the subject of a number of molecular mechanic studies.[4] The C–O bond lengths in the ring were in the range 1.402–1.443 Å. The mean C–O length from O(3) of 1.440 Å is slightly larger than the 1.415 Å from O(1). Although this difference is of relatively low significance it is consistent with the involvement of the ring ether oxygen atom O(3) in a strong intramolecular hydrogen bond to the 2-hydroxy substituent on the equatorial phenyl group at C(4), and indicated by the short distance of 1.98 Å between O(3) and H(42). The presence of such a hydrogen bond in 1,3-dioxanes bearing a 4-(2-hydroxyphenyl) substituent has been deduced from previously reported IR solution studies[5] and may be relevant to molecular interaction with the receptor

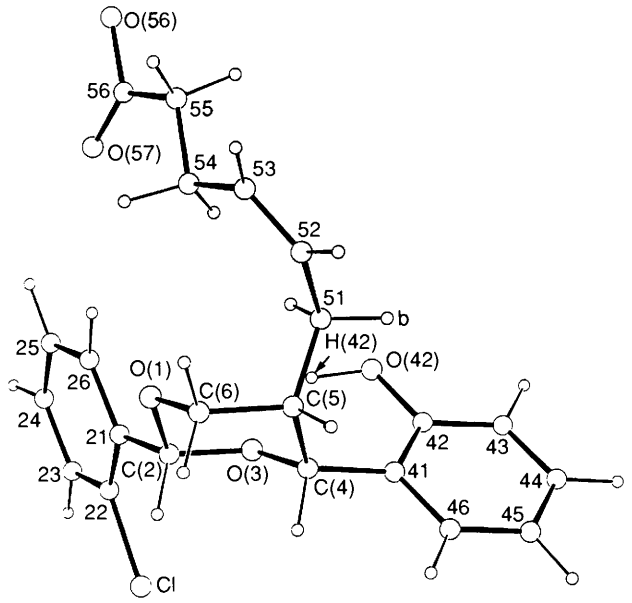


Figure 1. A perspective view of the crystal structure of (2). Selected bond lengths (Å): O(1)–C(2) 1.402(10), O(1)–C(6) 1.428(10), O(3)–C(2) 1.438(8), O(3)–C(4) 1.443(9), C(2)–C(21) 1.485(11), C(4)–C(5) 1.536(11), C(5)–C(6) 1.540(10), C(5)–C(51) 1.527(11), C(51)–C(52) 1.482(11), C(52–C(53) 1.317(11), C(53)–C(54) 1.500(14), C(54)–C(55) 1.467(15), C(55)–C(56) 1.498(15), C(56)–O(56) 1.295(14), C(56)–O(57) 1.199(15).

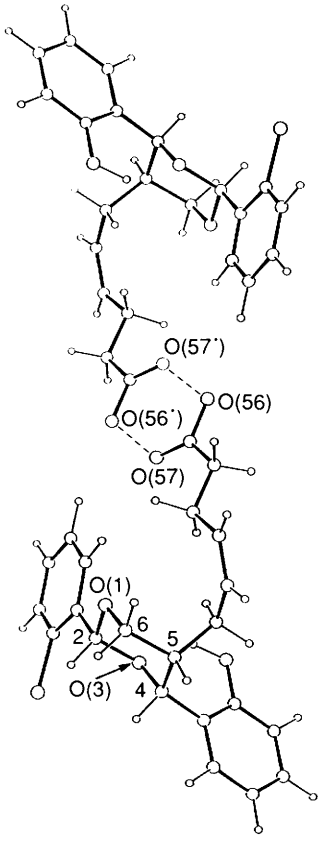


Figure 2. The centrosymmetric hydrogen-bonded dimeric unit in the solid state structure of (2) {O(56)••• O(57') 2.63 Å}.

site. Close analogues of (2), which lack the phenolic OH, are at least one order of magnitude less potent as TxA_2 antagonists.[3,5] It is thus conceivable that an alteration in molecular shape,

† Crystal data for compound (2). $C_{21}H_{22}ClO_5$, *M*, 389.85, monoclinic *a* = 19.452(4), *b* = 6.292(2), *c* = 17.333 (4) Å, β = 109.58(2), *U* = 1 998.8 Å^3, space group $P2_1/c$, *F*(000) = 820, μ(Mo-K_α) = 1.77 cm^{-1}, *Z* = 4, D_c = 1.295 g cm^{-3}. Data were collected on a Philips PW 1100 diffractometer in the θ-range 3–23°, using Mo-K_α radiation. A total of 2 485 reflections were recorded, and gave 1 101 unique reflections with $I/\sigma(I) > 3.0$. The structure was solved by direct methods.

The H-atoms attached to C-atoms were included at calculated positions and the phenyl groups were treated as rigid hexagonal rings (C–C 1.395 Å). The H-atom attached to the phenolic oxygen atom, O(42), was located in a subsequent difference-Fourier synthesis, but the carboxylic proton was not detected. The chlorine and oxygen atoms were assigned anisotropic thermal parameters in the full matrix refinement which converged at $R = 0.0606$ and $R_w = 0.0601$. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See 'Instructions for Authors (1990).' *J. Chem. Soc., Perkin Trans. 1*, 1990 Issue 1.

attendant upon the formation of the internal hydrogen bond in (**2**) produces a more effective binding interaction with the receptor.

The hexenoic acid side chain at C(5) of the dioxane ring had the axial orientation with the carboxyl group above the plane of the dioxane ring. This finding contrasts with X-ray structural studies[6] of thromboxane B_2 which has little if any TxA_2-like activity. In thromboxane B_2 the carboxylic acid side chain lies remote from and in the plane of its pyran ring system. The chlorophenyl ring was orientated out of the plane of the 1,3-dioxane ring so that the chlorine atom lay below the dioxane ring plane with respect to the C(5) substituent. [Torsion angle O(1), C(2), C(21), C(22) was −162.83°.]

Figure 2 shows the short contact distance between the carboxylic oxygen atoms [O(56)···O(57′)] = 2.63 Å) of adjacent molecules related by a crystallographic inversion centre, which indicates that the molecules exist as H-bonded dimers in the solid state.

References

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