Stereochemistry of Benzodiazepine Receptor Ligands. Possible Role of C–H ··· X Interactions in Drug–Receptor Binding and Crystal Structures of CL218–872, Zopiclone and DMCM

Valerio Bertolasi, Valeria Ferretti, and Gastone Gilli *
Centro di Strutturistica Diffrattometrica e Dipartimento di Chimica, Universitá di Ferrara, Italy
Pier Andrea Borea
Istituto di Farmacologia, Universitá di Ferrara, Italy

The crystal structures of three benzodiazepine (BDZ)-receptor ligands, *i.e.* CL218–872, Zopiclone and DMCM, are reported. CL218–872 crystallizes in the space group *Pccn* with a = 22.624(2), b = 13.073(2), c = 8.385(1) Å. 1 160 reflections with $I > 3\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined by weighted full-matrix least-squares with anisotropic non-H and isotropic H atoms to R = 0.038. Zopiclone crystallizes in the space group $P2_12_12_1$ with a = 5.567(3), b = 8.852(2), c = 35.677(17) Å. 915 reflections with $I > 1.5\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined by weighted full-matrix least-squares with anisotropic non-H and calculated H atoms to R = 0.060. DMCM crystallizes in the space group $P2_1/n$ with a = 13.801(3), b = 10.980(2), c = 10.620(2) Å, β = 103.81(2)°. 1 857 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined by weighted full-matrix least-squares with anisotropic non-H and isotropic H atoms to R = 0.044.

A detailed analysis of the hydrogen bonds (HB) which exist in the packing of the three crystals has been carried out in order to understand the role played by hydrogen-bond interactions in the mechanism of action in drug-receptor binding. The shortage of typical HB donor groups causes, in the structures examined, the occurrence of an unusual number of short C–H ··· X (X = O,N,F) interactions, where all hydrogens involved possess a partial positive charge, *i.e.* a somewhat acidic character. This fact can be an indication of the importance of such interactions, normally neglected. It is also shown, mainly by calculation of the electrostatic potential spanned by the single molecules, that the =N–N= group of the triazole ring in CL218–872 can play the role usually played by the strong acceptor C=O group present in almost all BDZ-receptor ligands.

Recently, several new drugs, chemically unrelated to benzodiazepines, have been found which can interact with high affinity with benzodiazepine receptors but which display pharmacological properties often different from those of benzodiazepines.[1] They belong to at least six chemical classes completely different from a stereochemical point of view yet binding with high efficiency to the same receptor where they are able to displace each other; moreover, they show a spectrum of biological activities ranging continuously from compounds having full benzodiazepine-like properties (agonists, AG) to those having completely opposite action (inverse agonists, IAG) to a third class of compound (antagonists, ANT) able to bind to benzodiazepine-receptors without producing, *per se*, any pharmacological effect. All these reasons make BDZ-receptor ligands ideal candidates for stereochemical modelling of drug–receptor interactions. In a recent paper[2] we have proposed a general model for such an interaction which is able to account for both binding abilities and kinds of biochemical and pharmacological activities. It is based on the assumption of a rather diffuse recognition site where the main drug-receptor interactions are mediated by the drug carbonylic or iminic groups *via* hydrogen bonding and the observed differences in pharmacological profiles are accounted for by the different localization of the different ligands inside this unique binding site.

The present paper reports the crystal structures of two agonists at the BDZ-receptor, *i.e.* Zopiclone[3] and CL218–872[4] belonging to the classes of cyclopyrrolones and triazolopyrazines, respectively, and DMCM,[1] a β-carboline which is considered to be the most powerful inverse agonist presently known. These structures have been determined in assessing the above BDZ-receptor model and accordingly some preliminary crystallographic data have been already reported.[2] We report here, in addition to the full structural data, an analysis of the crystal packing of these compounds in comparison with those of three other ligands at the same receptor, *i.e.* βCCM (a β-carboline)[5] and CGS8216 and CGS9896 (two pyrazoloquinolines).[6] It will be shown that the outcome of the packing analyses have definite chemical meaning and possible pharmacological implications in line with the results of a previous analysis of BDZ crystal packing.[7,8]

Results and Discussion

Crystal data, experimental details, and solution and refinement of the structures are reported in Table 1 and final co-ordinates in Tables 2–4. Bond distances and angles are given in Tables 5–7 and ORTEP[9] views of the molecules are shown in Figures 1–3.† The molecule of CL218–872 is nearly planar, the angles between the mean planes P1 [1,2,4-triazole ring, $\Sigma(\Delta/\sigma)^2$ = 1.44]; P2 [pyridazine ring, $\Sigma(\Delta/\sigma)^2$ = 160.99]; and P3 [phenyl ring,

† Tables of thermal parameters and hydrogen atom co-ordinates have been deposited at the Cambridge Crystallographic Data Centre. For details, see 'Instructions for Authors (1990),' *J. Chem. Soc., Perkin Trans. 2*, in the January issue.

Table 1. Crystal data, solution and refinement.[a]

Compound	CL218–872[b]	Zopiclone[c]	DMCM[d]
Formula	$C_{13}H_9F_3N_4$	$C_{17}H_{17}ClN_6O_3$	$C_{17}H_{18}N_2O_4$
M	278.24	388.82	314.34
Space group	*Pccn*	$P2_12_12_1$	$P2_1/n$
Cell parameters, a/Å	22.264(2)	5.567(3)	13.801(3)
b/Å	13.073(2)	8.852(2)	10.980(2)
c/Å	8.385(1)	35.677(17)	10.620(2)
β/°			103.81(2)
V/Å^3	2 440.6(6)	1 758(1)	1 562.8(6)
Z	8	4	4
D_{calc}/Mg m^{-3}	1.51	1.47	1.34
$F(000)$	1 136	808	664
μ(Mo-K_α)/mm^{-1}	0.09	0.25	0.09
Crystal size/mm^3	0.2 × 0.2 × 0.4	0.05 × 0.12 × 0.17	0.2 × 0.3 × 0.4
Independent reflections	2 661	1 846	3 405
Observed [$I > n\sigma(I)$]	1 160 (n = 3)	915 (n = 1.5)	1 857 (n = 2)
Refinement			
H atoms	isotropic	calculated	isotropic
non-H atoms	anisotropic	anisotropic	anisotropic
R_1, R_2	0.038, 0.045	0.060, 0.068	0.044, 0.047
Max. shift/error	0.06	0.06	0.07
Largest ΔF peak/e Å^{-3}	0.17	0.25	0.17
S	1.6	1.6	1.4
Number of variables	244	244	280

[a] Data collection instrument: Enraf–Nonius CAD4; T = 295 K; radiation: Mo-K_α (λ = 0.710 69 Å) graphite monochromated; ω/2θ scan; 25 centring reflections in the 10–14° θ range; 3 monitored reflections every 2 h; $\theta_{min}-\theta_{max}$ = 2.0–27°; solution by MULTAN82;[32] full-matrix refinement; $R_1 = \Sigma|\Delta F_o|/\Sigma|F_o|$, $R_2 = \{\Sigma w(\Delta F_o)^2/\Sigma w(F_o)^2\}^{\frac{1}{2}}$; weights: $w = 4F_o^2/\sigma^2(F_o^2) + (pF_o^2)^2$, p = 0.05, 0.08, 0.04 for CL218–872, Zopiclone and DMCM, respectively. All calculations performed by the CAD4 SDP system of programs;[33] scattering factors from ref. 34. [b] 3-Methyl-6-[3-trifluoromethylphenyl]-1,2,4-triazolo[4,3-*b*]pyridazine. [c] 6-(5-Chloro-2-pyridyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl]-4-methyl-piperazine-1-carboxylate. [d] 4-Ethyl-6,7-dimethoxy-3-methoxycarbonyl-9*H*-pyrido[3,4-*b*]indole.

Table 2. Positional (× 10^4) parameters with esds in parentheses for CL218–872.

Atom	x	y	z
F(1)[a]	6 105(2)	−1 581(2)	4 272(5)
F(2)[a]	7 032(2)	−1 740(3)	4 363(7)
F(3)[a]	6 521(2)	−1 928(2)	6 406(5)
F(11)[a]	6 031(2)	−1 664(2)	4 919(8)
F(21)[a]	6 846(3)	−1 596(3)	3 780(5)
F(31)[a]	6 817(2)	−2 024(2)	6 103(5)
N(1)	5 394.6(9)	5 395(1)	3 351(3)
N(2)	5 029(1)	4 646(1)	2 691(3)
N(3)	5 742.1(8)	3 929(1)	4 135(2)
N(4)	6 101.6(8)	3 218(1)	4 825(3)
C(1)	6 647(1)	−275(2)	5 532(3)
C(2)	7 104(1)	7(2)	6 534(4)
C(3)	7 176(1)	1 029(2)	6 919(4)
C(4)	6 796(1)	1 747(2)	6 267(4)
C(5)	6 337(1)	1 471(2)	5 242(3)
C(6)	6 262(1)	440(2)	4 882(3)
C(7)	6 574(1)	−1 380(2)	5 100(4)
C(8)	5 938(1)	2 267(2)	4 540(3)
C(9)	5 418(1)	2 006(2)	3 617(3)
C(10)	5 080(1)	2 731(2)	2 950(3)
C(11)	5 249(1)	3 764(2)	3 179(3)
C(12)	5 813(1)	4 965(2)	4 205(3)
C(13)	6 284(1)	5 477(2)	5 144(4)

[a] Occupancy: 0.5

Table 3. Positional (× 10^4) parameters with esds in parentheses for Zopiclone.

Atom	x	y	z
Cl	−3 025(5)	−6 283(3)	−1 071.7(8)
O(1)	6 148(12)	−3 590(8)	−2 170(2)
O(2)	4 538(11)	−535(6)	−1 271(2)
O(3)	1 607(11)	1 085(7)	−1 094(2)
N(1)	278(13)	−2 632(8)	−1 438(2)
N(2)	3 745(14)	−2 142(8)	−1 777(2)
N(3)	8 369(17)	−526(10)	−2 329(2)
N(4)	5 784(15)	1 661(9)	−1 910(2)
N(5)	4 548(13)	326(8)	−685(2)
N(6)	6 640(14)	216(8)	36(2)
C(1)	−989(17)	−5 116(9)	−1 302(2)
C(2)	−1 266(17)	−3 608(11)	−1 279(2)
C(3)	2 126(17)	−3 210(9)	−1 624(2)
C(4)	2 459(17)	−4 762(10)	−1 664(3)
C(5)	912(19)	−5 715(10)	−1 502(3)
C(6)	5 550(16)	−2 368(11)	−2 032(2)
C(7)	6 557(18)	−861(10)	−2 110(2)
C(8)	5 349(17)	190(10)	−1 900(3)
C(9)	3 624(16)	−580(9)	−1 642(2)
C(10)	8 834(21)	955(14)	−2 350(3)
C(11)	7 641(21)	2 020(12)	−2 151(3)
C(12)	3 451(15)	360(9)	−1 018(2)
C(13)	6 947(19)	−171(10)	−638(3)
C(14)	7 325(18)	−868(10)	−254(3)
C(15)	4 126(18)	636(12)	−14(3)
C(16)	3 743(18)	1 344(11)	−387(2)
C(17)	7 103(22)	−403(13)	407(3)

$\Sigma(\Delta/\sigma)^2$ = 16.33] being: P1–P2, 1.50(7); P1–P3, 8.25(10); and P2–P3, 7.99(8)°. The CF_3 group has been found to be disordered and best results were attained by refining two CF_3 groups, found in the ΔF synthesis and mutually rotated by an average angle of 29.3° with 0.5 occupancy factor. The packing is mainly controlled by short intermolecular C–H···N and C–H···F contacts: H(9)···N(1) ($1-x$, $\frac{1}{2}-y$, $\frac{1}{2}-z$), H(9)···N(2) ($1-x$, $y-\frac{1}{2}$, $\frac{1}{2}-z$) and H(10)···F(1) ($1-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$). Molecules are stacked in end-to-tail dimers related by a centre of symmetry and where only the two triazole

Table 4. Positional (× 10^4) parameters with esds in parentheses for DMCM.

Atom	*x*	*y*	*z*
O(1)	−151(1)	7 714(2)	4 488(2)
O(2)	1 428(1)	8 247(2)	4 745(2)
O(3)	−1 965(1)	1 975(2)	−734(2)
O(4)	−498(1)	925(1)	−1 364(2)
N(1)	1 764(1)	3 776(2)	1 429(2)
N(2)	1 898(1)	6 425(2)	3 558(2)
C(1)	86(1)	3 854(2)	1 178(2)
C(2)	−897(1)	3 437(2)	652(2)
C(3)	−1 050(2)	2 466(2)	−177(2)
C(4)	−234(2)	1 874(2)	−523(2)
C(5)	728(2)	2 247(2)	−8(2)
C(6)	868(1)	3 231(2)	833(2)
C(7)	537(1)	4 827(2)	2 039(2)
C(8)	1 575(1)	4 721(2)	2 167(2)
C(9)	2 228(1)	5 533(2)	2 934(2)
C(10)	900(1)	6 530(2)	3 452(2)
C(11)	179(1)	5 764(2)	2 698(2)
C(12)	645(2)	7 527(2)	4 259(2)
C(13)	1 284(2)	9 173(3)	5 637(3)
C(14)	−2 812(2)	2 531(3)	−448(3)
C(15)	292(2)	292(3)	−1 744(2)
C(16)	−932(1)	5 878(2)	2 577(2)
C(17)	−1 292(2)	5 016(3)	3 493(2)

Table 5. Bond distances/Å and bond angles/° with esds in parentheses for CL218–872.

Bond distances			
F(1)–C(7)	1.281(5)	C(1)–C(2)	1.370(4)
F(2)–C(7)	1.282(5)	C(1)–C(6)	1.380(4)
F(3)–C(7)	1.314(5)	C(1)–C(7)	1.498(4)
F(11)–C(7)	1.274(5)	C(2)–C(3)	1.384(4)
F(21)–C(7)	1.293(6)	C(3)–C(4)	1.377(4)
F(31)–C(7)	1.307(5)	C(4)–C(5)	1.383(4)
N(1)–N(2)	1.388(3)	C(5)–C(6)	1.391(4)
N(1)–C(12)	1.302(3)	C(5)–C(8)	1.490(4)
N(2)–C(11)	1.318(3)	C(8)–C(9)	1.434(3)
N(3)–N(4)	1.356(2)	C(9)–C(10)	1.333(4)
N(3)–C(11)	1.376(3)	C(10)–C(11)	1.415(4)
N(3)–C(12)	1.365(3)	C(12)–C(13)	1.472(4)
N(4)–C(8)	1.317(3)		
Bond angles			
N(2)–N(1)–C(12)	109.5(2)	F(2)–C(7)–C(1)	112.6(3)
N(1)–N(2)–C(11)	106.0(2)	F(3)–C(7)–C(1)	109.5(3)
N(4)–N(3)–C(11)	127.7(2)	F(11)–C(7)–F(21)	106.2(4)
N(4)–N(3)–C(12)	126.4(2)	F(11)–C(7)–F(31)	106.4(3)
C(11)–N(3)–C(12)	105.8(2)	F(11)–C(7)–C(1)	114.4(2)
N(3)–N(4)–C(8)	114.0(2)	F(21)–C(7)–F(31)	102.5(3)
C(2)–C(1)–C(6)	121.4(2)	F(21)–C(7)–C(1)	111.5(3)
C(2)–C(1)–C(7)	119.2(2)	F(31)–C(7)–C(1)	114.9(3)
C(6)–C(1)–C(7)	119.4(2)	N(4)–C(8)–C(5)	115.0(2)
C(1)–C(2)–C(3)	119.3(2)	N(4)–C(8)–C(9)	123.1(2)
C(2)–C(3)–C(4)	119.6(2)	C(5)–C(8)–C(9)	121.9(2)
C(3)–C(4)–C(5)	121.5(2)	C(8)–C(9)–C(10)	120.9(2)
C(4)–C(5)–C(6)	118.4(2)	C(9)–C(10)–C(11)	118.1(2)
C(4)–C(5)–C(8)	120.3(2)	N(2)–C(11)–N(3)	109.9(2)
C(6)–C(5)–C(8)	121.3(2)	N(2)–C(11)–C(10)	134.0(2)
C(1)–C(6)–C(5)	119.7(2)	N(3)–C(11)–C(10)	116.2(2)
F(1)–C(7)–F(2)	108.2(4)	N(1)–C(12)–N(3)	108.8(2)
F(1)–C(7)–F(3)	105.5(3)	N(1)–C(12)–C(13)	127.4(2)
F(1)–C(7)–C(1)	114.7(2)	N(3)–C(12)–C(13)	123.8(2)
F(2)–C(7)–F(3)	105.8(3)		

rings are facing in such a way that the N(1) atom forms the closest contacts with all the other atoms of the five-membered ring belonging to the other molecule [N(1)···N(1′) = 3.435(3), N(1)···N(2′) = 3.451(4), N(1)···N(3′) = 3.410(3), N(1)···C(11′) = 3.425(3), and N(1)···C(12′) = 3.413(3) Å]. The interaction is probably dipolar in nature, because an analysis of bond distances shows the determinant contribution of the polar canonical forms $N(3)^+$=C(12)–$N(1)^-$, $N(3)^+$=C(11)–$N(2)^-$ and $N(3)^+$=N(4)–C(8)=C(9)–C(10)=C(11)–$N(2)^-$. Moreover, it can be expected that the region in front of the N(1)–N(2) bond and in the plane of the molecule will be particularly rich in electron density.

The Zopiclone molecule can be divided into two fragments.

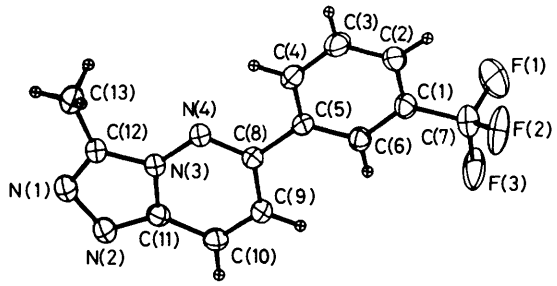

Figure 1. An ORTEP view of CL218–872 showing the thermal ellipsoids at 30% probability.

Table 6. Bond distances/Å and bond angles/° with esds in parentheses for Zopiclone.

Bond distances			
Cl–C(1)	1.740(9)	N(5)–C(13)	1.416(13)
O(1)–C(6)	1.234(12)	N(5)–C(16)	1.464(11)
O(2)–C(9)	1.419(10)	N(6)–C(14)	1.462(12)
O(2)–C(12)	1.345(10)	N(6)–C(15)	1.459(13)
O(3)–C(12)	1.241(10)	N(6)–C(17)	1.456(13)
N(1)–C(2)	1.344(12)	C(1)–C(2)	1.346(13)
N(1)–C(3)	1.327(11)	C(1)–C(5)	1.382(14)
N(2)–C(3)	1.416(11)	C(3)–C(4)	1.394(12)
N(2)–C(6)	1.370(11)	C(4)–C(5)	1.337(14)
N(2)–C(9)	1.466(11)	C(6)–C(7)	1.474(13)
N(3)–C(7)	1.310(12)	C(7)–C(8)	1.371(13)
N(3)–C(10)	1.338(15)	C(8)–C(9)	1.495(13)
N(4)–C(8)	1.325(12)	C(10)–C(11)	1.354(16)
N(4)–C(11)	1.382(14)	C(13)–C(14)	1.517(15)
N(5)–C(12)	1.336(10)	C(15)–C(16)	1.486(13)
Bond angles			
C(9)–O(2)–C(12)	118.8(7)	O(1)–C(6)–N(2)	126.2(9)
C(2)–N(1)–C(3)	117.3(7)	O(1)–C(6)–C(7)	128.0(8)
C(3)–N(2)–C(6)	128.7(7)	N(2)–C(6)–C(7)	105.8(7)
C(3)–N(2)–C(9)	118.3(7)	N(3)–C(7)–C(6)	127.6(8)
C(6)–N(2)–C(9)	112.9(7)	N(3)–C(7)–C(8)	123.4(9)
C(7)–N(3)–C(10)	113.8(9)	C(6)–C(7)–C(8)	108.9(8)
C(8)–N(4)–C(11)	112.3(8)	N(4)–C(8)–C(7)	124.2(8)
C(12)–N(5)–C(13)	122.9(8)	N(4)–C(8)–C(9)	125.6(8)
C(12)–N(5)–C(16)	119.5(7)	C(7)–C(8)–C(9)	110.0(8)
C(13)–N(5)–C(16)	113.2(7)	O(2)–C(9)–N(2)	108.5(6)
C(14)–N(6)–C(15)	109.3(7)	O(2)–C(9)–C(8)	109.4(7)
C(14)–N(6)–C(17)	110.5(8)	N(2)–C(9)–C(8)	101.4(7)
C(15)–N(6)–C(17)	112.2(8)	N(3)–C(10)–C(11)	123.9(11)
Cl–C(1)–C(2)	119.0(7)	N(4)–C(11)–C(10)	122.2(10)
Cl–C(1)–C(5)	121.0(6)	O(2)–C(12)–O(3)	122.0(7)
C(2)–C(1)–C(5)	120.0(8)	O(2)–C(12)–N(5)	112.2(7)
N(1)–C(2)–C(1)	122.6(8)	O(3)–C(12)–N(5)	125.7(8)
N(1)–C(3)–N(2)	115.4(7)	N(5)–C(13)–C(14)	111.4(8)
N(1)–C(3)–C(4)	122.3(8)	N(6)–C(14)–C(13)	109.6(7)
N(2)–C(3)–C(4)	122.3(8)	N(6)–C(15)–C(16)	110.8(8)
C(3)–C(4)–C(5)	119.5(9)	N(5)–C(16)–C(15)	110.3(8)
C(1)–C(5)–C(4)	118.3(8)		

The first includes the pyrrolopyrazine and chloropyridine rings and seems to be the most important part for the biological activity as it is almost perfectly superimposable onto other benzodiazepine-receptor ligands such as CGS8216 and CGS9896;[5,6] the second fragment is the *N*-piperazine carboxylate group which has been supposed to play an important role in increasing the agonistic properties of the first part of the molecule.[2] The whole first fragment is essentially planar, the angles between the mean planes P1 = pyridine, P2 = pyrrole and P3 = pyrazine being: P1–P2, 13.5(3); P2–P3, 3.9(3); P1–P3, 9.6(3)°; the average plane through the carbamic group is nearly perpendicular to the mean P1–P3 plane. The piperazine ring adopts a chair conformation with Q = 0.56(1) Å, Φ = 177(1), θ = 5.3(9)°;[10] the N(6) atom is pyramidal (average C–N–C angle of 110.7°) whereas the carbamic N(5) atom is rather flat [average C–N–C angle = 118.5°, τ = 5.9(9)°, χ_N = 25.2(9)°, χ_C = −1.8(9)° in the carbamic group].[11] The packing is characterized by short C–H···O contacts which will be discussed later [C(5)–H(5)···O(3) (x, $y-1$, z)]; C(10)–H(10)···O(1) (2 − x, y + ½, − z − ½); C(13)–H(13)···O(3) (1 + x, y, z)].

The structure of DMCM is comparable to those of other β-carbolines.[5,12,13] The molecule is remarkably planar with

Table 7. Bond distances/Å and bond angles/° with esds in parentheses for DMCM.

Bond distances			
O(1)–C(12)	1.198(3)	C(1)–C(7)	1.447(3)
O(2)–C(12)	1.339(3)	C(2)–C(3)	1.367(3)
O(2)–C(13)	1.436(4)	C(3)–C(4)	1.422(4)
O(3)–C(3)	1.371(3)	C(4)–C(5)	1.372(4)
O(3)–C(14)	1.414(4)	C(5)–C(6)	1.386(3)
O(4)–C(4)	1.364(3)	C(7)–C(8)	1.411(2)
O(4)–C(15)	1.430(4)	C(7)–C(11)	1.399(3)
N(1)–C(6)	1.383(2)	C(8)–C(9)	1.386(3)
N(1)–C(8)	1.363(3)	C(10)–C(11)	1.399(2)
N(2)–C(9)	1.323(3)	C(10)–C(12)	1.484(3)
N(2)–C(10)	1.360(2)	C(11)–C(16)	1.513(2)
C(1)–C(2)	1.414(2)	C(16)–C(17)	1.523(4)
C(1)–C(6)	1.398(3)		
Bond angles			
C(12)–O(2)–C(13)	116.5(2)	C(1)–C(6)–C(5)	123.6(2)
C(3)–O(3)–C(14)	117.4(2)	C(1)–C(7)–C(8)	105.9(2)
C(4)–O(4)–C(15)	117.0(2)	C(1)–C(7)–C(11)	135.2(2)
C(6)–N(1)–C(8)	108.6(2)	C(8)–C(7)–C(11)	119.0(2)
C(9)–N(2)–C(10)	119.0(2)	N(1)–C(8)–C(7)	109.7(2)
C(2)–C(1)–C(6)	117.8(2)	N(1)–C(8)–C(9)	129.9(2)
C(2)–C(1)–C(7)	135.7(2)	C(7)–C(8)–C(9)	120.4(2)
C(6)–C(1)–C(7)	106.5(2)	N(2)–C(9)–C(8)	121.2(2)
C(1)–C(2)–C(3)	119.6(2)	N(2)–C(10)–C(11)	124.4(2)
O(3)–C(3)–C(2)	124.7(2)	N(2)–C(10)–C(12)	113.0(2)
O(3)–C(3)–C(4)	114.4(2)	C(11)–C(10)–C(12)	122.7(2)
C(2)–C(3)–C(4)	120.8(2)	C(7)–C(11)–C(10)	116.1(2)
O(4)–C(4)–C(3)	114.5(2)	C(7)–C(11)–C(16)	119.4(2)
O(4)–C(4)–C(5)	124.8(2)	C(10)–C(11)–C(16)	124.5(2)
C(3)–C(4)–C(5)	120.7(2)	O(1)–C(12)–O(2)	121.0(2)
C(4)–C(5)–C(6)	117.5(2)	O(1)–C(12)–C(10)	126.8(2)
N(1)–C(6)–C(5)	127.2(2)	O(2)–C(12)–C(10)	112.2(2)
N(1)–C(6)–C(5)	127.2(2)	C(11)–C(16)–C(17)	111.9(2)

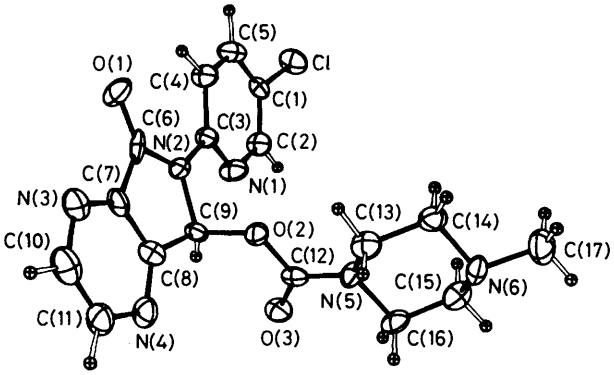

Figure 2. An ORTEP view of Zopiclone showing the thermal ellipsoids at 30% probability.

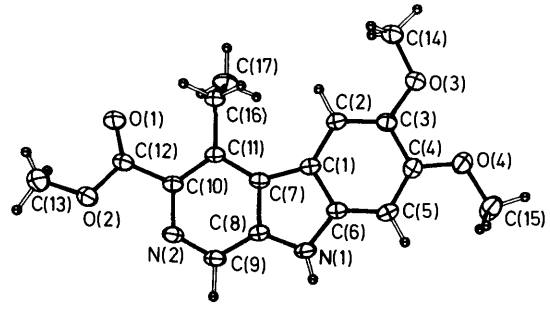

Figure 3. An ORTEP view of DMCM showing the thermal ellipsoids at 30% probability.

Table 8. Intermolecular distances/Å and angles/° for D–H···A–B interactions in the structures in Figure 4. Esds in parentheses.

Structure	H-bond	D–H	H···A	D···A	D–H···A	C–H···X[a] interaction type	Ref.
CL218–872	C(9)–H(9)···N(1)	0.95(1)	2.52(2)	3.230(3)	131(1)	2a···5b	Present work
	C(9)–H(9)···N(2)	0.95(1)	2.50(2)	3.422(2)	161(1)	2a···5b	
	C(10)–H(10)···F(1)	0.92(2)	2.57(2)	3.353(5)	143(1)	2a···4b	
Zopiclone	C(5)–H(5)···O(3)	(0.95)[b]	2.47	3.21(1)	132	4a···2b	Present work
	C(10)–H(10)···O(1)	(0.95)[b]	2.35	3.30(1)	161	1a···1b	
	C(13)–H(13)···O(3)	(0.95)[b]	2.52	3.26(1)	132	3a···2b	
DMCM	N(1)–H(N1)···O(2)	0.81(3)	2.41(3)	3.099(3)	144(2)	—	Present work
	N(1)–H(N1)···N(2)	0.81(3)	2.53(2)	3.172(3)	138(2)	—	
	C(9)–H(9)···O(4)	1.03(1)	2.54(2)	3.442(2)	146(2)	1a···3b	
βCCM	C(A9)–H(A9)···O(B1)	0.91(4)	2.74(4)	3.388(6)	129(3)	1a···2b	2
	C(B9)–H(B9)···O(A1)	0.93(4)	2.40(4)	3.095(7)	131(3)	1a···2b	
	N(B1)–H(NB1)···N(A2)	0.86(6)	2.55(6)	3.307(6)	147(4)	—	
CGS8216	N(3)–H(30)···O	0.97(3)	1.72(3)	2.694(3)	175(2)	—	3
	C(16)–H(16)···O	0.95(3)	2.69(3)	3.358(3)	127(2)	phenyl···1a	
CGS9896	N(3)–H(30)···O	0.87(3)	1.90(3)	2.766(4)	173(3)	—	3
	C(16)–H(16)···O	0.88(3)	2.64(3)	3.323(5)	136(3)	phenyl···1a	

[a] See Fig. 5. [b] H calculated.

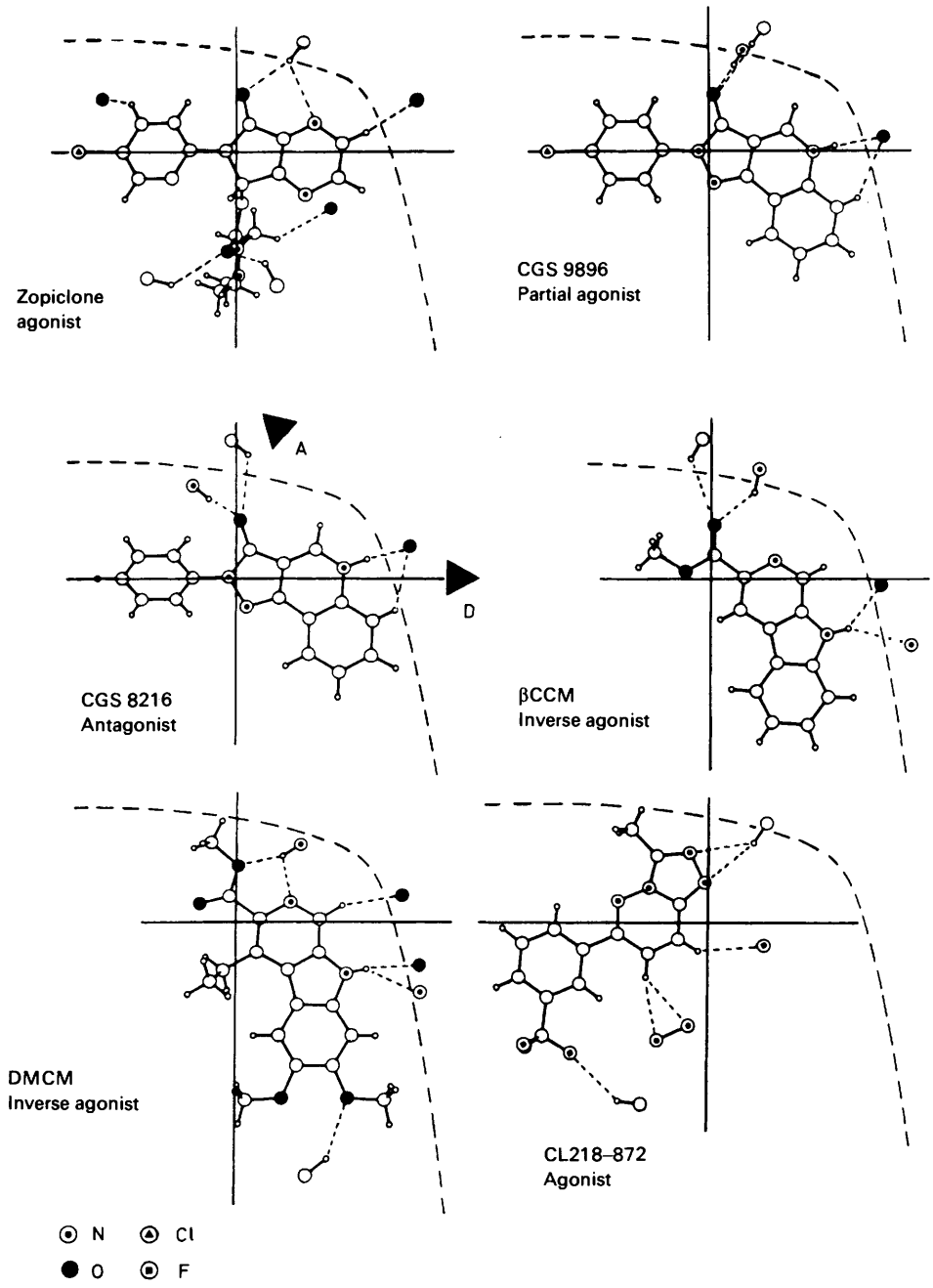

Figure 4. Scheme of HB interactions for the BDZ-receptor ligands taken into account. Molecules are drawn following the modalities given in ref. 1, with the exception of CL218–872. The dashed lines represent the model binding site with fixed HB interactions (A and D).

the exception of the C(17) atom. Angles between planes C(1)–C(6) = P1 [$\Sigma(\Delta/\sigma)^2$ = 49.3], C(1), C(6)–C(8), N(1) = P2 [$\Sigma(\Delta/\sigma)^2$ = 28.6] and N(2), C(7)–C(11) = P3 [$\Sigma(\Delta/\sigma)^2$ = 14.4] are P1–P2, 0.87(6); P2–P3, 0.73(7) and P1–P3, 1.50(6)°. The two methoxy and the methoxycarbonyl groups lie on the average plane as shown by the torsion angles C(2)–C(3)–O(3)–C(14), 1.3(4); C(5)–C(4)–O(4)–C(15), −1.0(4); and N(2)–C(10)–C(12)–O(2), 10.9(3)°. The conformation around the C(10)–C(12) bond is N(2), O(2)-*cis* which is at variance with βCCM [5] where it was found to be *trans* while the methoxy group was *syn* in both cases. The coplanarity is an indication of the π delocalization throughout the whole molecule. In order to understand better the role played by hydrogen bonding in the mechanism of action of benzodiazepine-receptor ligands, a complete analysis of the HB interactions occurring in the packing of the structures has been carried out. Compounds belonging to different chemical classes have been considered at the same time with the assumption that the recognition site is unique for all ligands, as previously suggested.[2] Table 8 reports the geometrical features of the hydrogen bonds formed, including those involving C–H···X short interactions. A common feature of these molecules, as far as HB interactions are concerned, is the constant excess of HB-acceptors with respect to HB-donors. Such an excess suggests that these crystals would conform themselves to the rule, given by Taylor and Kennard,[14] that the hydrogen bond arrangements will tend to include as many acceptors as possible but with a definite preference for the strong acceptors, which will form H bonds even with weak donors; in particular, it would be foreseen that C–H groups will be implied as HB-donors wherever possible.

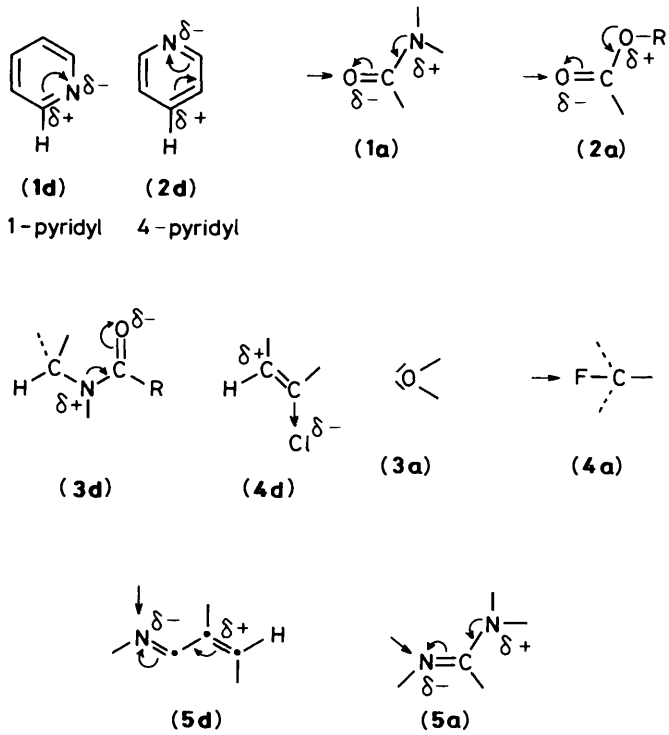

Figure 5. Chemical groups implied as typical donors (**1d**)–(**5d**) or acceptors (**1a**)–(**5a**) in C–H···X hydrogen bonds observed in the structures investigated. C–H···X interactions with hydrogens belonging to simple phenyl groups have not been classified.

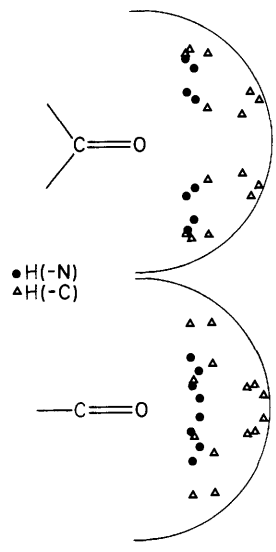

Figure 6. Scatterplots (viewed in two perpendicular directions) showing the positions of H-donor atoms involved in HBs to the oxygen of the carbonyl groups in some of the molecules discussed.

Figure 4 shows the complete scheme of hydrogen bond interactions on the molecules considered. As expected, the oxygen atoms, which are stronger HB-acceptors, are more involved in hydrogen bonds than the weaker nitrogens; the ratio between the groups actually acting as HB-acceptors over the total number of possibly implied groups is 7:10 for oxygen and 4:10 for nitrogen. Moreover, the shortage of typical HB-donor groups, such as –N–H or –O–H, causes the occurrence of an unusual number of short C–H···X (X=O,N,F) interactions. Though the fact that the C–H groups can be involved in short intermolecular contacts of HB type with acceptor oxygens or nitrogens was observed by Sutor[15] in 1963, the use of the expression 'C–H hydrogen bond' has been considered with scepticism for a long time. Only recently has a systematic analysis on crystal structures of organic compounds determined by neutron diffraction[16] established beyond question that some C–H···X interactions, formed by C–H groups with more acidic character, have characteristics typical of H-bonds. These interactions are supposed to play an important role in biological systems by conferring additional stabilization to classical hydrogen bonds[17–19] and further analysis of the coulombic and van der Waals packing energy terms carried out in some molecular crystals[20] was able to show that C–H···X interactions actually contribute to the stabilization of some specific packing arrangements. Taking into account the accepted van der Waals radii[21] of 1.20, 1.70, 1.55, 1.52, and 1.47 Å for H, C, N, O, and F atoms, respectively, we may classify as C–H···X hydrogen bonds those contacts which have the following parameters: H···X < 2.75 Å, C···X < 3.50 Å and 120 < C–H···X < 180°. Using this criterion eleven C–H···X HBs are found in the six structures examined which are phenomenologically reducible into two different types: (*a*) the acceptor is bonded only to the donor C–H group or (*b*) it is interacting with another typical HB-donor (N–H) (Table 8). The chemical situations liable to produce the observed C–H···X interactions can be reduced to those shown in Figure 5; from the figure we have omitted only two other C–H···O interactions in CGS8216 and CGS9896 which are rather weak; these occur in support of a strong N–H···O hydrogen bond in which the HB-donors are phenyl hydrogens. All hydrogens involved do have a partial positive charge and, in some way, an acidic character, caused by resonance or inductive effects; on the other hand, all the HB-acceptors are strong electronegative groups. It may be added that such a pattern of C–H···X interactions has been confirmed in recent crystal structures of other two benzodiazepine-receptor ligands: 7-phenyltriazolo[4,3-*b*]pyridazine[22] and Suriclone[23] belonging to the chemical classes of triazolopyridazines (as CL218–872) and cyclopyrrolones (as Zopiclone) respectively. The geometrical features of the short contacts involving both C–H and N–H hydrogens with the carbonyl group are summarized in Figure 6; it may be of interest to remark that both groups show a common tendency to lie in the directions usually ascribed to sp^2 lone-pairs,[14,24] though hydrogen-bond distances for contacts involving C–H groups are longer.

Biochemical Implications.—Since hydrogen bonds often are the most relevant interactions between ligands and binding sites in biological systems, it is worthwhile to assume that HB interactions found in the crystals are in some way representative of the possible drug–receptor HB interactions. The six molecules we are dealing with are drawn in Figure 4 in the orientation in which they are supposed to bind to the receptor site, according to the drug–receptor interactions model we proposed elsewhere;[2] only the CL218–872 orientation has been slightly modified. The model suggested that the receptor site was bent (dashed line in Figure 4) and that agonists, antagonists and inverse agonists were binding in positions progressively shifted from upper left to lower right but using fixed hydrogen-bond interaction points, *i.e.* a main HB accepted in A and an accessory HB donated in D (see Figure 4). This model-binding site substantially agrees with that proposed for a more restricted set of drugs by Codding and Muir.[25] Compound CL218–872 is difficult to locate in the receptor model owing to the lack of a typical HB-acceptor, such as oxygen, always present in the other ligands considered. However, it has been already mentioned that the delocalization on the heterocyclic system induces negative partial charges on both N(1) and N(2) triazole atoms, a

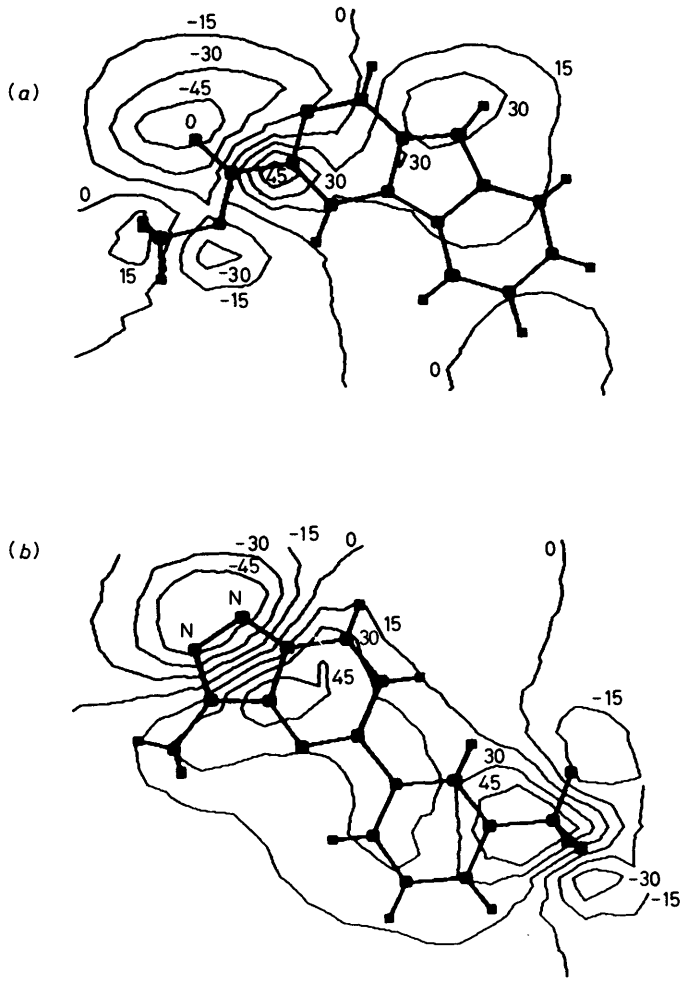

Figure 7. Sections of the electrostatic map parallel to the mean plane of the molecules and passing (*a*) through O and (*b*) through N–N groups, respectively. V^{ES} in kcal mol^{-1}.

charge arrangement which is favourable to the involvement of both negative nitrogens in a strong bifurcated C–H hydrogen bond. Comparison of CL218–872 with other benzodiazepine-receptor ligands makes it seem reasonable that the hypothesis that the =N–N= group of the triazole ring can play, as far as the electrostatic properties are concerned, the same role otherwise played by the carbonyl group. This hypothesis is supported by the existence of active triazolo–benzodiazepines and hetero-diazepines (such as alprazolam, estazolam, brotizolam) the crystal structures[26–29] of which show that the position of the more common C=O group of benzodiazepin-2-ones is occupied by the two nitrogens of the triazole ring. The idea of a strong negative charge localized on the triazole =N–N= fragment can be confirmed by calculating the electrostatic potential spanned by the CL218–872 molecule which can be obtained for any point R from the partial atomic charges q_i located on any different atom at position R_i, as $V^{ES}(R) = \Sigma_i q_i/|R_i - R|$. The q_i values have been calculated by INDO quantum mechanical calculations.[30] Its graphical representation, carried out by the CHEM-X system of programs,[31] is shown in Figure 7(*b*). The electrostatic map shows, in the =N–N= region, a negative potential zone as high as 45 kcal mol^{-1}. For comparison Figure 7(*a*) shows the same map for βCCM which displays near the C=O group a negative minimum of almost exactly the same entity.

Acknowledgements

The authors are indebted to Dr. J. W. Epstein, American Cyanamid, Lederle Laboratories (Pearl River, NY) for supplying crystals of CL218–872; to Drs. J. Mollé and J. C. Blanchard, Rhone-Poulenc Recherches (Vitry-sur-Seine, France) for supplying crystals of Zopiclone and Dr. R. Schmiechen, Schering AG (Berlin, Germany) for supplying crystals of DMCM.

References

1 C. Braestrup, M. Nielsen, T. Honoré, L. H. Jensen, and E. M. Petersen, *Neuropharmacology*, 1983, **22**, 1451.
2 P. A. Borea, G. Gilli, V. Bertolasi, and V. Ferretti, *Mol. Pharmacol.*, 1987, **31**, 334.
3 J. C. Blanchard, A. Boireau, C. Garrett, and L. Julon, *Life Sci.*, 1979, **24**, 2417.
4 C. A. Klepner, A. S. Lippa, D. I. Benson, M. C. Sano, and B. Beer, *Pharmacol., Biochem. and Behav.*, 1979, **11**, 457.
5 V. Bertolasi, V. Ferretti, G. Gilli, and P. A. Borea, *Acta Crystallogr., Sect. C*, 1984, **40**, 1981.
6 V. Ferretti, V. Bertolasi, G. Gilli, and P. A. Borea, *Acta Crystallogr., Sect. C*, 1985, **41**, 107.
7 P. A. Borea, G. Gilli, V. Bertolasi, and M. Sacerdoti, *Biochem. Pharmacol.*, 1982, **31**, 889.
8 P. A. Borea and G. Gilli, *Arzeneim. Forsch.*, 1984, **34**, 649.
9 C. K. Johnson, 'ORTEP', Report ORLN-5138, 3rd. rev., Oak Ridge National Laboratory, Tennessee, USA, 1976.
10 D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, 1975, **97**, 1354.
11 F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.*, 1971, **59**, 169.
12 P. W. Codding, *Can. J. Chem.*, 1983, **61**, 529.
13 A. K. S. Muir and P. W. Codding, *Can. J. Chem.*, 1984, **62**, 1803.
14 R. Taylor and O. Kennard, *Acc. Chem. Res.*, 1984, **17**, 320.
15 J. Sutor, *J. Chem. Soc.*, 1963, 1105.
15 R. Taylor and O. Kennard, *J. Am. Chem. Soc.*, 1982, **104**, 5063.
17 W. Saenger, *Angew. Chem.*, 1973, **86**, 690.
18 G. A. Jeffrey and H. Maluszynska, *Int. J. Biol. Macromol.*, 1982 **4**, 173.
19 R. L. Ornstein and J. R. Fresco, *Proc. Natl. Acad. Sci. USA*, 1983, **80**, 5171.
20 Z. Berkovitch-Yellin and L. Leiserowitz, *Acta Crystallogr., Sect. B*, 1984, **40**, 159.
21 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.
22 T. Boulanger, L. Ledent, D. P. Vencaunteren, B. Norberg, G. Evrard, and F. Durant, *Acta Crystallogr., Sect. C*, 1988, **44**, 1759.
23 P. W. Codding, M. B. Szkaradzinska, and N. L. Duke, *Acta Crystallogr., Sect. C*, 1988, **44**, 1938.
24 P. Murray-Rust and J. P. Glusker, *J. Am. Chem. Soc.*, 1984, **106**, 1018.
25 P. W. Codding and A. K. S. Muir, *Mol. Pharmacol.*, 1985, **28**, 343.
26 J. B. Hoster, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1971, 1609.
27 K. Kamiya, Y. Wada, and M. Nishikawa, *Chem. Pharm. Bull.*, 1973, **21**, 1520.
28 H. J. Butcher and T. A. Hamor, *Acta Crystallogr., Sect. C*, 1985, **41**, 265.
29 H. J. Kemmish and T. A. Hamor, *Acta Crystallogr., Sect. C.*, 1988, **44**, 1823.
30 A. Chung-Phillips, 'CNINDO-DYNAM', *QCPE*, 274.
31 CHEM-X, released July 1987, Chemical Design Ltd., Oxford, UK.
32 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, 'MULTAN82. A system of Computer Programs for the Automatic Solution of Crystal Structures from *X*-Ray Diffraction Data,' Universities of York, England, and Louvain, Belgium, 1982.
33 B. A. Frenz, in 'Computing in Crystallography,' eds. H. Schenk, R. Olthof-Hazekamp, H. Van Koningsveld, and G. C. Bassi, Delft University Press, 1978, p. 44.
34 D. T. Cromer and J. T. Waber, 'International Tables for *X*-Ray Crystallography,' Kynock Press, Birmingham, UK, 1974, vol. 4.

Paper 9/01226E
Received 21*st March* 1989
Accepted 7*th September* 1989