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Letters to the Editor

Dipole-mediated hydrogen bonding interactions between cimetidine analogues and the histamine H_2 receptor

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In 1986 we reported (Young et al 1986) the results of an investigation to rationalize the differences in the in-vitro H_2 receptor histamine antagonist activities of a series of analogues of cimetidine in which the cyanoguanidine group had been replaced by other polar H-bonding moieties. For all 13 active compounds, antagonist activity (determined on the isolated atrium of the guinea-pig) was found to be highly correlated with the orientation of the group's dipole moment and with lipophilicity, as shown in equation 1 (Table 1), where K_B represents the apparent dissociation constant of the drug-receptor complex, P is the octanol/water partition coefficient for the neutral form of the antagonist, and θ is a measure of the deviation of the group's dipole orientation (ψ) from the proposed optimum angle of 30°, as defined previously (Young et al 1986), calculated using the CNDO/2 molecular orbital method (see Table 2). Further support for the validity of equation 1 was provided by its successful use in predicting the inactivity of two further analogues. In contrast, neither the magnitude of the experimental dipole moment (μ_{exp}) measured in water, nor the dipole moment vector term, $\mu_{exp} \cos \theta$, were found to have general significance in relation to antagonist activity.

It has recently been suggested (Donné-Op den Kelder 1987), however, that dipole moments measured in water, a medium of high dielectric, may not be appropriate when considering drug interactions with protein-borne receptors, and that their use in combination with the theoretically derived quantity, cos θ, is inappropriate because the calculation of θ is performed on an isolated molecule in the absence of solvent. The use of water as the solvent for dipole moment measurements was, however, dictated by the relative insolubility of the cyanoguanidine and other model compounds used (Young et al 1982), and the relevance of these dipole moments to H_2 receptor binding is, of course, open to question. We have therefore compared our original result with correlations using theoretically derived values for both μ and θ for the cyanoguanidine and other polar groups.

From the CNDO/2 calculations performed to derive the values of θ, we also obtained the dipole moments (μ) shown in Table 1. Comparison of H_2 antagonist activity with μ or $\mu \cos \theta$ for the 13 compounds again failed to give a significant correlation (eqns 3 and 4, Table 2),

Table 1. Correlation equations for H_2 antagonist activity in 13 analogues.

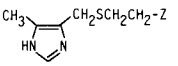
	r	s	eqn
$-\log K_B = 9{\cdot}1\ (\pm 2{\cdot}9) \cos\theta + 0{\cdot}60\ (\pm 0{\cdot}46) \log P - 2{\cdot}7\ (\pm 2{\cdot}6)$	0·91	0·41	(1)
$-\log K_B = 9{\cdot}1\ (\pm 3{\cdot}8) \cos\theta - 2{\cdot}7\ (\pm 3{\cdot}4)$	0·85	0·53	(2)
$-\log K_B = 0{\cdot}11\ (\pm 0{\cdot}35)\ \mu + 4{\cdot}7\ (\pm 2{\cdot}8)$	0·20	0·99	(3)
$-\log K_B = 0{\cdot}23\ (\pm 0{\cdot}28)\ \mu \cos\theta + 3{\cdot}8\ (\pm 2{\cdot}1)$	0·47	0·89	(4)
$-\log K_B = 0{\cdot}20\ (\pm 0{\cdot}34)\ \mu' + 4{\cdot}1\ (\pm 2{\cdot}6)$	0·35	0·94	(5)
$-\log K_B = 0{\cdot}24\ (\pm 0{\cdot}28)\ \mu' \cos\theta' + 3{\cdot}9\ (\pm 2{\cdot}0)$	0·49	0·88	(6)
$-\log K_B = 8{\cdot}6\ (\pm 5{\cdot}3) \cos\theta' - 2{\cdot}2\ (\pm 4{\cdot}8)$	0·73	0·69	(7)
$-\log K_B = 9{\cdot}6\ (\pm 3{\cdot}9) \cos\theta' + 0{\cdot}84\ (\pm 0{\cdot}57) \log P - 3{\cdot}2\ (\pm 3{\cdot}6)$	0·88	0·50	(8)

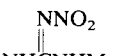
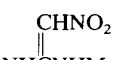
while cos θ alone gave a highly significant correlation (eqn 2). As an added check, we have calculated dipole parameters (μ' and cos θ') using the MNDO molecular orbital method assuming the planar configuration of each of the polar groups (see Table 2) and compared these with antagonist data. As before, μ' and $\mu' \cos \theta'$ failed to correlate with antagonist activity (eqns 5 and 6), while cos θ' alone gave a highly significant correlation (eqn 7), but with a lower correlation coefficient than that for equation 2. Inclusion of the log P term in equation 8 gave an improved relationship of similar statistical significance to our original equation (eqn 1).

To give a physical interpretation to the cos θ term in equation 1, we proposed (Young et al 1986) that the group, Z, has an orientational function, and assists in the establishment of hydrogen-bonded interactions with the H_2 receptor. In free energy terms, the H-bonding contribution to receptor binding might be given by equation 9:

$$-\log K_B \propto \Delta G_{\text{H-bonding}} \cos \theta \qquad (9)$$

Table 2. Physical properties and H_2 receptor antagonist activities.



Z	$-\log K_B$[a]	logP[a]	μ (CNDO/2)[b]	μ′ (MNDO)[c]	cos θ (CNDO/2)[d]	cos θ′ (MNDO)[d]
	6·10	0·40	7·63	6·78	0·96	0·95
	5·84	0·13	9·39	8·05	0·96	0·95
	5·85	−0·40	8·10	8·13	1·00	1·00
	6·04	0·55	5·66	5·94	0·87	0·87
	4·69	−0·06	4·52	3·93	0·87	0·87
	7·31	1·04	7·40	7·58	1·00	0·98
	6·31	−0·87	7·94	8·02	1·00	0·99
	4·21	−0·5	7·99	6·79	0·81	0·83
	5·13	0·02	9·61	7·64	0·88	0·93
	4·80	0·8	8·63	6·89	0·82	0·79
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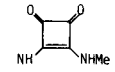
	4·57	−0·74	8·26	9·94	0·87	0·94
	4·23	−0·08	7·15	5·28	0·71	0·73

[a] Taken from Young et al 1986.
[b] CNDO/2 program No. 261, Quantum Chemistry Program Exchange, Indiana University Chemistry Department, Bloomington, IN. Molecules created in COSMIC framework (Vinter et al 1987).
[c] MNDO program of Stewart (1983) within MOPAC suite.
[d] cos θ and cos θ′ defined as 30-ψ, where ψ is the angle subtended by the dipole and the last C–N bond in the side chain.

Although no physical data on the comparative H-bonding abilities of these groups is available, they are all very effective H-bond donors. Within this series of analogues, therefore, the variation in the ΔG term may be small compared to that in the cos θ term so that it would not attain statistical significance in the correlation, and can probably be ignored.

Equations 1–8 clearly support our original proposal

that the orientation of the dipole in the cyanoguanidine or replacement group in relation to the side chain, and not the dipole moment or its 30° vector, explains most of the variance in the in-vitro H_2 antagonist activity in this series of analogues.

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Penetration of diazepam and the non-peptide CCK antagonist, L-364,718, into rat brain

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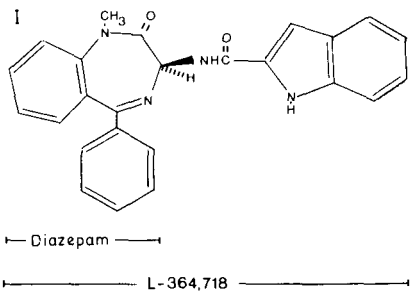
Interest in the actions of the peptide cholecystokinin (CCK) has led to the design and synthesis of several non-peptide CCK antagonists, the most recent being that produced by Merck Sharp & Dohme and designated L-364,718. This can be viewed as modified D-tryptophan linked to diazepam (1-methyl-3-(2-indoloyl)amino-5-phenyl-3*H*-1,4-benzodiazepin-2-one) I.

The compound has an affinity for CCK receptors in the rat pancreas and bovine gallbladder which almost equals CCK itself, and it is an extremely potent CCK antagonist (Chang & Lotti 1986). For example, it will competitively antagonize CCK-induced contractions of the guinea-pig isolated ileum and colon with a pA_2 of 9·9. It will also antagonize the CCK-induced inhibition of gastric emptying in the mouse, with an ED50 of 0·04 mg kg^{-1} (Chang et al 1986; Evans et al 1986).

It has been suggested that CCK may also be a central neurotransmitter (Dockray 1976) and, therefore, the entry of L-364,718 into the brain is of interest since this is a prerequisite for any CNS action. We have investigated the penetration of L-364,718 into brain from blood by measuring its Brain Uptake Index (BUI) as first described by Oldendorf (1970). Since the compound has structural similarities to diazepam (see I) which is known to act on the CNS, we have also measured the BUI for diazepam, for comparative purposes.

Male Wistar rats, 350–500 g were anaesthetized with sodium pentobarbitone (Sagatal, 50 mg kg^{-1} i.p.). The left common carotid artery was surgically exposed and catheterized with a length of Portex pp50 tubing. A 1 mL syringe containing 250 μL of injectate was attached to the tubing. The animal was positioned supine in a guillotine and the injectate administered in a single bolus. The injectate had the composition (mM): Na^+ 148, K^+ 4, Ca^{2+} 2, Cl^- 155, buffered to pH 7·4 with 4 mM Tris. Each 250 μL contained 0·25 μCi of 4-iodo [N-methyl-^{14}C]antipyrine (sp. act. = 55 mCi $mmol^{-1}$, Amersham International), which was the reference solute to which the cerebral capillary was highly permeable, and either 1·0 μCi of [*N*-methyl-^{3}H]diazepam (sp. act. = 80 Ci $mmol^{-1}$, Amersham International) or 1·0 μCi of [*N*-methyl-^{3}H]-L-364,718 (sp. act. = 67 Ci $mmol^{-1}$, Merck Sharp & Dohme) which were test solutes.



Twelve seconds after the administration of the injectate the rat was decapitated and the brain removed. The cerebellum and brain stem were freed from the cerebral hemispheres which were then separated by a single mid-sagittal cut. The left hemisphere was further dissected into cerebral cortex, hippocampus, midbrain and hypothalamus, and striatum according to Glowinski & Iversen (1966). A single tissue sample of about 100 mg was taken from each of these four regions and prepared for scintillation counting by transference to preweighed scintillation vials, which were reweighed, and to each of which was added 1 mL of Amersham NCS tissue solubilizer. The vials were left for 12 h at 45 °C then 10 mL of Amersham OCS scintillant and 30 μL of glacial acetic acid were added to each with shaking. Vials containing 5 μL of injectate were also

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