molecule, out of which eight of molecule (I) and nine of molecules (II) and (III) are involved in N—H···O-type bonding.

The configurational similarities between sulphate and phosphate ions make it possible to extrapolate the observations made in the present study to the possible mode of binding of arcaine molecules to nucleic acids. The inter-sulphate distance of 7·26 Å along the *a* axis can be compared with that of 7·3 Å between successive phosphate groups along the helix in polynucleotides. As in the previous studies we observe that the amine molecule has the correct geometry to bridge in DNA helices through hydrogen bonds with the phosphate ions of the nucleic acids, stabilizing their structures.

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Structures of Two 2-Arylpyrazolo[4,3-*c*]quinolin-3-ones: CGS8216, $C_{16}H_{11}N_3O$, and CGS9896, $C_{16}H_{10}ClN_3O$*

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Abstract. CGS8216, 2-phenyl-2,5-dihydropyrazolo-[4,3-*c*]quinolin-3(3*H*)-one, $M_r = 261{\cdot}28$, $P2_1/c$, $a = 8{\cdot}147\ (2)$, $b = 12{\cdot}855\ (2)$, $c = 12{\cdot}521\ (3)$ Å, $\beta = 103{\cdot}62\ (2)°$, $V = 1274{\cdot}4\ (5)$ Å^3, $Z = 4$, $D_x = 1{\cdot}36$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}08$ mm^{-1}, $F(000) = 544$, $T = 298$ K, $R = 0{\cdot}037$ for 1147 unique observed reflections. CGS9896, 2-(4-chlorophenyl)-2,5-dihydropyrazolo[4,3-*c*]quinolin-3(3*H*)-one, $M_r = 295{\cdot}73$, *Pbca*, $a = 14{\cdot}790\ (3)$, $b = 9{\cdot}515\ (1)$, $c = 18{\cdot}326\ (3)$ Å, $V = 2578{\cdot}9\ (7)$ Å^3, $Z = 8$, $D_x = 1{\cdot}52$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}29$ mm^{-1}, $F(000) = 1216$, $T = 298$ K, $R = 0{\cdot}046$ for 1117 unique observed reflections. The crystal packing of the two compounds is discussed. It is shown that intermolecular hydrogen bonding can cause small but significant changes in the geometry of the –HN–C=C–C=O fragment. The role played by these compounds as benzodiazepine-receptor ligands in the central nervous system is briefly reviewed.

Introduction. The central nervous system contains stereospecific saturable high-affinity recognition sites for benzodiazepines (BDZ's), which are thought to mediate their pharmacological effects (Squires & Braestrup, 1977; Möhler & Okada, 1977). There is evidence that BDZ's exert their action mainly *via* the GABA system (GABA = γ-aminobutyric acid) (Braestrup, Nielsen, Honoré, Jensen & Petersen, 1983), the molecular basis of this interaction being probably the GABA–BDZ-receptor-chloride channel complex. BDZ's are widely employed in therapeutics as anxiolytic and anticonvulsant agents. More recently, several new drugs have been discovered interacting with BDZ

* Stereochemistry of Benzodiazepine-Receptor Ligands. II. Part I: Bertolasi, Ferretti, Gilli & Borea (1984).

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receptors but whose pharmacological effects *in vivo* may differ from BDZ's themselves (Braestrup *et al.*, 1983). According to their method of action they are classified as BDZ agonists (anxiolytics, anticonvulsants), antagonists (able to antagonize BDZ's effects without any significant *per se* biological effect) and inverse agonists (anxiogenics, convulsants). We have already remarked (Bertolasi, Ferretti, Gilli & Borea, 1984) that, from a pure stereochemical point of view, agonists, antagonists and inverse agonists must possess a common chemical moiety responsible for the binding, while agonists and inverse agonists should have other steric features able to trigger their specific biological effects. This makes these compounds potentially an ideal test for structure–properties relationships.

We report here the crystal and molecular structures of two BDZ-receptor ligands belonging to the class of pyrazoloquinolinones, *i.e.* CGS8216, an almost pure BDZ antagonist, and CGS9896, displaying partial BDZ agonist behaviour (Yokoyama, Ritter & Neubert, 1982; Braestrup *et al.*, 1983; Brown & Martin, 1983).

Experimental. CGS8216: Crystals kindly provided by Dr H. Schröter, CIBA–GEIGY Ltd, Basel, Switzerland, recrystallized from ethanol. Yellow crystal $0{\cdot}14 \times 0{\cdot}18 \times 0{\cdot}31$ mm submitted to analysis; Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$ radiation, $\omega/2\theta$ scan ($2 \le \theta \le 27°$); cell parameters from 25 reflections $9 < \theta < 13°$; 2780 reflections collected ($0 \le h \le 10$, $0 \le k \le 16$, $-16 \le l \le 16$), 1147 having $I_o \ge 3\sigma(I_o)$ used in refinement; two standard reflections monitored every 2 h, no significant variations during data collection. Solution by direct methods (*MULTAN*81; Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1981); refinement by full-matrix least squares on F, anisotropic non-H and isotropic H atoms (from ΔF synthesis), final $R = 0{\cdot}037$ and $R_w = 0{\cdot}044$, $1/w^2 = \sigma^2(I_o) + 0{\cdot}05\,|F_o|^2$, max. $\Delta/\sigma = 0{\cdot}08$, $S = 1{\cdot}2$; final difference map peaks $-0{\cdot}1$–$0{\cdot}1$ e Å^{-3}.

CGS9896: Crystals from same source recrystallized from ethanol. Yellow crystal $0{\cdot}10 \times 0{\cdot}29 \times 0{\cdot}36$ mm submitted to analysis; Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$ radiation, $\omega/2\theta$ scan ($2 \le \theta \le 26°$); cell parameters from 25 reflections $10 < \theta < 13°$; 2529 reflections collected ($0 \le h \le 18$, $0 \le k \le 11$, $0 \le l \le 22$), 1117 having $I_o \ge 2\sigma(I_o)$ used in refinement; two standard reflections monitored every 2 h showed no significant variations during data collection. Solution by direct methods (*MULTAN*81); refinement by full-matrix least squares on F, anisotropic non-H and isotropic H atoms (from ΔF synthesis), final $R = 0{\cdot}046$, $R_w = 0{\cdot}049$, $1/w^2 = \sigma^2(I_o) + 0{\cdot}05\,|F_o|^2$; max. $\Delta/\sigma = 0{\cdot}01$, $S = 1{\cdot}4$; final difference map peaks $-0{\cdot}23$–$0{\cdot}25$ e Å^{-3}. Scattering factors from *International Tables for X-ray Crystallography* (1974); all calculations performed with CAD-4 *SDP* system of programs (Frenz, 1978) and *PARST* (Nardelli, 1983).

Discussion. Atomic parameters for both structures are given in Table 1* and the corresponding bond distances and angles in Tables 2 and 3; the molecules are shown in Figs. 1 and 2. Both distances and endocyclic angles (not involving H's) of CGS8216 and CGS9896 agree within the 3σ limit. The pattern of bond distances shows remarkable contributions of the polar canonical forms $\overset{\oplus}{N}(1)=C(7)-\overset{\ominus}{O}$ and $\overset{\oplus}{N}(3)=C(10)-C(8)=C(7)-\overset{\ominus}{O}$. In particular, the contribution of the latter is such that the N(3)–C(10) 'single'-bond distance [on average 1·323 (4) Å] is shorter than the C(8)–C(10) 'double'-bond distance [on average 1·363 (5) Å]. The effect can be ascribed to the fact that C=O and N–H are implied in infinite chains of CO···HN hydrogen bonds (see packing); this causes a partial obliteration of the partial charges and a consequent increased contribution of the polar canonical form. A similar case has been discussed by Bechtel, Chasseau, Gaultier & Hauw (1976) for a series of β-naphthoquinones. The pyrazoloquinoline moiety is nearly planar, the angles between the mean planes $P1$[C(7)–C(9), N(2), N(1)], $P2$[C(8)–C(12), N(3)] and $P3$[C(11)–C(16)] being $P1$–$P2 = 4{\cdot}65$ (9) and 4·2 (1)°, $P2$–$P3 = 4{\cdot}51$ (8) and 2·8 (1)°, $P1$–$P3 = 9{\cdot}14$ (9) and 6·1 (2)° for CGS8216 and CGS9896 respectively. The two molecules differ mainly in the conformation of the C(1)–C(6) phenyl ring, the torsion angle N(2)–N(1)–C(4)–C(5) being −41·2 (4) and 10·2 (5)° in CGS8216 and CGS9896. The difference is probably caused by the packing arrangement as discussed below.

The packing is somewhat different in the two crystals. In CGS8216 (Fig. 3) molecules are arranged in infinite columns running along **y**, linked head-to-tail by hydrogen bonds C(7)=O···H–N(3) $(2-x, -\frac{1}{2}+y, \frac{3}{2}-z)$ and N(3)–H···O=C(7) $(2-x, \frac{1}{2}+y, \frac{3}{2}-z)$ [N···O = 2·694 (3), N–H = 0·97 (3), H···O = 1·72 (3) Å, N–H···O = 175 (2)°], which are strengthened by possible C(16)–H···O interactions [same symmetry operations: C···O = 3·358 (3), C–H = 0·95 (3) Å, H···O = 2·69 (3) Å, C–H···O = 127 (2)°]. The columns are packed by weak van der Waals forces, the only short contact being C(15)···C(10) $(x, \frac{1}{2}-y, \frac{1}{2}+z)$, 3·306 (3) Å. In CGS9896 the arrangement in columns of molecules linked by hydrogen bonds [C(7)=O···H–N(3) $(2-x, -\frac{1}{2}+y, \frac{3}{2}-z)$: N···O = 2·766 (4), N–H = 0·87 (3), H···O = 1·90 (3) Å, N–H···O = 173 (3)°] and C(16)–H···O

* Lists of structure factors and anisotropic thermal parameters for both compounds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39734 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional* ($\times 10^4$ *for non-*H*'s,* $\times 10^3$ *for* H*'s) and thermal* (Å^2 $\times 10^3$) *parameters with e.s.d.'s in parentheses*

U_{eq} according to Hamilton (1959).

	CGS8216				CGS9896			
	x	*y*	*z*	U_{eq}/U(Å^2)	*x*	*y*	*z*	U_{eq}/U(Å^2)
Cl					4941·5 (8)	−2710 (1)	4991·3 (9)	56·1 (6)
O	9145 (2)	−1264 (1)	6991 (1)	69 (4)	8977 (2)	−438 (3)	6468 (2)	40 (2)
N(1)	7764 (2)	−1371 (2)	8430 (2)	53 (1)	7563 (2)	398 (4)	6821 (2)	31 (2)
N(2)	7385 (2)	−737 (2)	9261 (2)	54 (1)	7185 (2)	1406 (4)	7304 (2)	32 (2)
N(3)	9473 (2)	1924 (2)	8433 (2)	54 (1)	9532 (2)	3122 (4)	8011 (2)	36 (2)
C(1)	6110 (4)	−4449 (2)	8167 (3)	91 (2)	5725 (3)	−1796 (5)	5516 (2)	38 (2)
C(2)	5991 (4)	−3863 (2)	7245 (3)	81 (2)	6614 (3)	−2231 (5)	5544 (2)	38 (2)
C(3)	6528 (3)	−2843 (2)	7317 (2)	64 (1)	7231 (2)	−1513 (5)	5965 (2)	35 (2)
C(4)	7204 (3)	−2418 (2)	8345 (2)	53 (1)	6964 (3)	−351 (4)	6359 (2)	30 (2)
C(5)	7310 (3)	−3001 (2)	9274 (2)	63 (2)	6075 (3)	97 (5)	6321 (2)	45 (3)
C(6)	6761 (4)	−4019 (2)	9183 (3)	85 (2)	5453 (3)	−640 (5)	5903 (3)	49 (3)
C(7)	8664 (3)	−872 (2)	7781 (2)	53 (1)	8497 (3)	384 (5)	6833 (2)	34 (2)
C(8)	8862 (3)	155 (2)	8222 (2)	48 (1)	8726 (3)	1465 (4)	7340 (2)	30 (2)
C(9)	8034 (3)	168 (2)	9103 (2)	48 (1)	7885 (3)	2009 (4)	7601 (2)	30 (2)
C(10)	9591 (3)	1032 (2)	7930 (2)	52 (1)	9523 (3)	2065 (4)	7541 (2)	35 (2)
C(11)	8593 (3)	2014 (2)	9266 (2)	50 (1)	8743 (3)	3666 (4)	8330 (2)	33 (2)
C(12)	7910 (3)	1136 (2)	9658 (2)	48 (1)	7888 (3)	3107 (4)	8137 (2)	31 (2)
C(13)	7068 (3)	1264 (2)	10500 (2)	59 (1)	7127 (3)	3658 (5)	8492 (2)	39 (3)
C(14)	6903 (3)	2233 (2)	10921 (2)	67 (1)	7209 (3)	4711 (5)	9004 (2)	45 (3)
C(15)	7539 (3)	3100 (2)	10496 (2)	68 (2)	8053 (3)	5246 (5)	9170 (2)	43 (2)
C(16)	8400 (3)	2999 (2)	9685 (2)	61 (1)	8812 (3)	4750 (5)	8838 (2)	39 (3)
H(1)	568 (3)	−516 (2)	808 (2)	110 (10)				
H(2)	555 (3)	−411 (2)	649 (2)	97 (9)	677 (2)	−297 (3)	525 (2)	18 (9)
H(3)	641 (3)	−237 (2)	664 (2)	84 (8)	785 (2)	−183 (3)	595 (2)	26 (10)
H(5)	772 (3)	−267 (2)	996 (2)	69 (7)	589 (3)	87 (5)	661 (2)	51 (13)
H(6)	689 (3)	−439 (2)	986 (2)	89 (8)	488 (3)	−16 (6)	584 (3)	99 (18)
H(10)	1023 (2)	105 (2)	735 (2)	54 (6)	1012 (2)	183 (4)	738 (2)	37 (11)
H(13)	659 (3)	63 (2)	1080 (2)	61 (6)	655 (2)	325 (4)	838 (2)	37 (11)
H(14)	631 (3)	230 (2)	1152 (2)	81 (8)	665 (3)	507 (4)	922 (2)	50 (12)
H(15)	738 (3)	378 (2)	1074 (2)	70 (7)	810 (2)	602 (4)	950 (2)	36 (11)
H(16)	881 (3)	361 (2)	941 (2)	80 (8)	935 (2)	507 (4)	895 (2)	31 (10)
H(30)	998 (3)	256 (2)	824 (2)	75 (7)	1002 (2)	357 (4)	814 (2)	51 (12)

Table 2. *Bond distances* (Å) *with e.s.d.'s in parentheses*

	CGS8216	CGS9896		CGS8216	CGS9896
Cl–C(1)		1·739 (4)	C(5)–C(6)	1·379 (4)	1·387 (6)
O–C(7)	1·252 (3)	1·250 (5)	C(7)–C(8)	1·426 (4)	1·427 (6)
N(1)–N(2)	1·412 (4)	1·420 (5)	C(8)–C(9)	1·422 (4)	1·430 (6)
N(1)–C(4)	1·417 (4)	1·418 (5)	C(8)–C(10)	1·364 (4)	1·361 (6)
N(1)–C(7)	1·375 (4)	1·382 (5)	C(9)–C(12)	1·440 (4)	1·434 (5)
N(2)–C(9)	1·312 (4)	1·303 (5)	C(11)–C(12)	1·398 (4)	1·417 (6)
N(3)–C(10)	1·323 (4)	1·324 (5)	C(11)–C(16)	1·394 (4)	1·393 (6)
N(3)–C(11)	1·403 (4)	1·404 (5)	C(12)–C(13)	1·396 (4)	1·402 (6)
C(1)–C(2)	1·363 (5)	1·379 (6)	C(13)–C(14)	1·372 (4)	1·378 (6)
C(1)–C(6)	1·374 (5)	1·369 (7)	C(14)–C(15)	1·387 (4)	1·382 (6)
C(2)–C(3)	1·378 (4)	1·376 (6)	C(15)–C(16)	1·370 (4)	1·361 (6)
C(3)–C(4)	1·387 (3)	1·378 (6)			
C(4)–C(5)	1·369 (4)	1·384 (6)			
N(3)–H(30)	0·97 (3)	0·87 (3)			
C–H (average)	0·98 [1]	0·95 [1]			

Table 3. *Bond angles* (°) *with e.s.d.'s in parentheses*

	CGS8216	CGS9896
N(2)–N(1)–C(4)	118·8 (2)	117·8 (3)
N(2)–N(1)–C(7)	113·9 (2)	113·0 (3)
C(4)–N(1)–C(7)	127·3 (2)	129·0 (4)
N(1)–N(2)–C(9)	103·6 (2)	104·2 (3)
C(10)–N(3)–C(11)	122·2 (2)	122·8 (4)
Cl–C(1)–C(2)		120·4 (3)
Cl–C(1)–C(6)		119·5 (3)
C(2)–C(1)–C(6)	119·8 (3)	120·1 (4)
C(1)–C(2)–C(3)	120·8 (3)	120·3 (4)
C(2)–C(3)–C(4)	119·1 (3)	120·1 (3)
N(1)–C(4)–C(3)	119·6 (2)	122·5 (4)
N(1)–C(4)–C(5)	120·1 (2)	118·0 (4)
C(3)–C(4)–C(5)	120·3 (2)	119·5 (4)
C(4)–C(5)–C(6)	119·7 (2)	120·1 (4)
C(1)–C(6)–C(5)	120·4 (3)	119·8 (4)
O–C(7)–N(1)	126·1 (2)	124·4 (4)
O–C(7)–C(8)	130·6 (2)	131·6 (4)
N(1)–C(7)–C(8)	103·3 (2)	103·9 (4)
C(7)–C(8)–C(9)	106·3 (2)	105·8 (4)
C(7)–C(8)–C(10)	132·7 (2)	133·2 (4)
C(9)–C(8)–C(10)	121·0 (2)	120·8 (4)
N(2)–C(9)–C(8)	112·8 (2)	113·1 (4)
N(2)–C(9)–C(12)	128·1 (2)	127·6 (4)
C(8)–C(9)–C(12)	119·0 (2)	119·4 (4)
N(3)–C(10)–C(8)	120·3 (2)	120·2 (4)
N(3)–C(11)–C(12)	120·7 (2)	120·0 (3)
N(3)–C(11)–C(16)	118·5 (2)	119·4 (4)
C(12)–C(11)–C(16)	120·8 (2)	120·7 (4)
C(9)–C(12)–C(11)	116·7 (2)	116·6 (4)
C(9)–C(12)–C(13)	124·7 (2)	126·0 (4)
C(11)–C(12)–C(13)	118·5 (2)	117·4 (4)
C(12)–C(13)–C(14)	120·5 (2)	121·2 (4)
C(13)–C(14)–C(15)	120·2 (2)	119·8 (4)
C(14)–C(15)–C(16)	120·7 (2)	121·2 (4)
C(11)–C(16)–C(15)	119·2 (2)	119·7 (4)

interactions [$(2-x, -\frac{1}{2}+y, \frac{3}{2}-z$): C···O = 3·323 (5), C—H = 0·88 (3), H···O = 2·64 (3) Å, C—H···O = 136 (3)°] is similar. In this case the small value of the N(2)—N(1)—C(4)—C(5) torsion angle allows a more efficient packing. It is achieved by the graphitic interchain packing shown in Fig. 4, where the relevant intermolecular contacts (assuming tentatively 3·30 and 3·50 Å as nonbonded C—N and C—C distances) are marked as dashed lines. They are N(1)···C(12^{I}) = 3·318 (5), C(2)···C(7^{I}) = 3·280 (6), C(3)···N(2^{I}) =

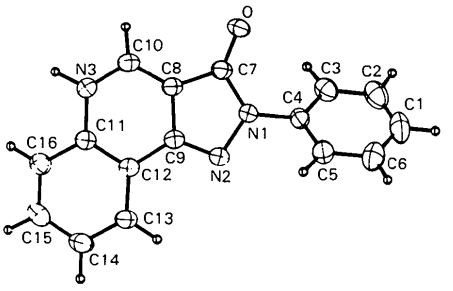

Fig. 1. An *ORTEP* (Johnson, 1971) view of the CGS8216 molecule displaying the thermal ellipsoids at 40% probability.

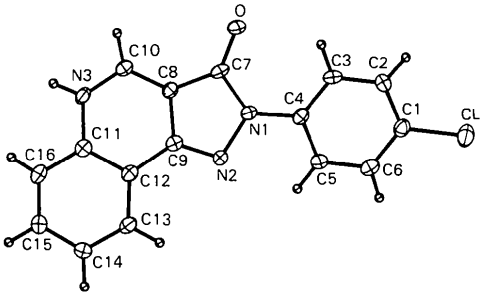

Fig. 2. An *ORTEP* (Johnson, 1971) view of the CGS9896 molecule displaying the thermal ellipsoids at 40% probability.

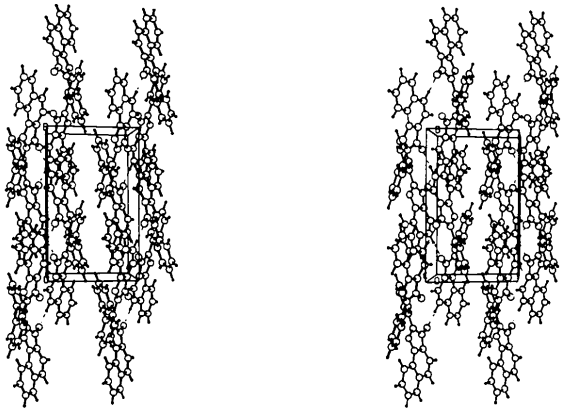

Fig. 3. A stereoscopic view of the crystal structure of CGS8216 along the *c* axis.

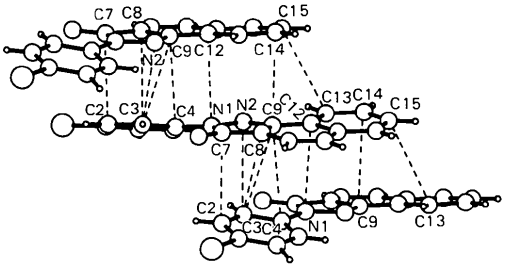

Fig. 4. Side view of the projection along the normal to the mean plane of the CGS9896 molecule. The three molecules (from the top) correspond to symmetry operations $(\frac{1}{2}-x+1, y-\frac{1}{2}, z)$, (x, y, z), $(\frac{1}{2}-x+1, y+\frac{1}{2}, z)$. Short contacts are shown as dashed lines.

3·269 (6), C(3)···C(8^{i}) = 3·472 (6), C(3)···C(9^{i}) = 3·316 (5), C(4)···C(9^{i}) = 3·397 (5), C(9)···C(14^{i}) = 3·378 (6), C(13)–C(15^{i}) = 3·486 (7) Å, where (i) stands for $(\frac{3}{2}-x, -\frac{1}{2}+y, z)$. The only other short contact is C(16)···Cl $(\frac{3}{2}-x, -y, \frac{1}{2}+z)$, 3·411 (5) Å.

Although chemically very similar CGS8216 and CGS9896 behave differently from a pharmacological point of view. The binding ability to BDZ receptors of the first (K_i for ^{3}H-diazepam binding *in vitro* = 0·3 n*M*) is three times lower than that of the latter (K_i = 0·1 n*M*) (Borea, 1984) though both are to be classified as strong binders (the mean K_i for clinically employed BDZ's ranges from 2 to 100 n*M*). Most importantly CGS8216 is only an antagonist, that is it sticks to the receptor site preventing agonists (*e.g.* BDZ's) from binding but not producing any *per se* biological effect. Conversely, CGS9896 both binds and produces an anxiolytic and anticonvulsant effect though milder than BDZ's themselves, *i.e.* it is a partial agonist. As the two compounds differ only in the substituent at C(1) it seems reasonable to assume that substitution in such a position plays an important role in triggering the agonist effect. This is confirmed by the fact that CGS9895 [the C(1)-methoxy derivative] displays a pharmacological profile similar to that of CGS9896 (Yokoyama *et al.*, 1982).

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