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Stereochemistry of Serotonin Receptor Ligands from Crystallographic Data. Crystal Structures of NAN-190.HBr, 1-Phenylbiguanide, MDL 72222 and Mianserin.HCl and Selectivity Criteria towards 5-HT_1, 5-HT_2 and 5-HT_3 Receptor Subtypes

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Abstract

The crystal and molecular structures of the following serotoninergic drugs have been determined: (1) 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine hydrobromide hemihydrate (NAN-190.HBr), $C_{23}H_{28}N_3O_3^+.Br^-.1/2H_2O$, M_r = 483.42, monoclinic, $C2/c$, a = 21.916 (4), b = 15.207 (2), c = 14.052 (2) Å, β = 101.56 (1)°, V = 4588 (1) Å^3, Z = 8, D_x = 1.40 Mg m^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 1.823 mm^{-1}, F(000) = 2008, T = 295 K, R = 0.035 for 2617 observed reflections; (2) *N*-phenylimidocarbonimidic diamide (1-phenylbiguanide), $C_8H_{11}N_5$, M_r = 177.21, monoclinic, $P2_1/c$, a = 9.781 (2), b = 35.040 (5), c = 11.000 (2) Å, β = 97.72 (1)°, V = 3736 (1) Å^3, Z = 16, D_x = 1.26 Mg m^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 0.084 mm^{-1}, F(000) = 1504, T = 295 K, R = 0.070 for 3407 observed reflections; (3) 8-methyl-8-azabicyclo[3.2.1.]oct-3-yl 3,5-dichlorobenzoate (MDL 72222), $C_{15}H_{17}Cl_2NO_2$, M_r = 314.21, triclinic, $P\bar{1}$, a = 8.480 (3), b = 9.840 (3), c = 10.158 (4) Å, α = 90.04 (3), β = 111.77 (3), γ = 105.07 (3)°, V = 755.6 (5) Å^3, Z = 2, D_x = 1.38 Mg m^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 0.430 mm^{-1}, F(000) = 328, T = 295 K, R = 0.070 for 1685 observed reflections; (4) 1,2,3,4,10,14b-hexahydro-2-methyldibenzo[c,f]pyrizino[1,2-a]azepine hydrochloride (mianserin.HCl), $C_{18}H_{21}N_2^+.Cl^-$, M_r = 300.83, monoclinic, $P2_1/a$, a = 9.014 (2), b = 14.917 (2), c = 12.412 (2) Å, β = 108.84 (1)°, V = 1579.5 (5) Å^3, Z = 4, D_x = 1.26 Mg m^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 0.237 mm^{-1}, F(000) = 640, T = 295 K, R = 0.063 for 1493 observed reflections. A systematic structural analysis of the present compounds and others known to interact with the 5-HT_1, 5-HT_2 and 5-HT_3 receptors allows to identify their similarities with the endogenous ligand serotonin (5-HT) and the stereochemical differences which determine selectivity for the various receptor subtypes. The pharmacophoric feature for 5-HT receptor binding is identified in a constant-length vector linking an aromatic ring with a protonated nitrogen, while specific affinities for receptorial subtypes and the nature of the effect appear to be modulated by the dimensions of the substituents at nitrogen.

1. Introduction

The endogenous ligand 5-hydroxytryptamine (5-HT or serotonin) is involved in several physiological events occurring at the peripheral level and in the central nervous system by interacting with specific serotoninergic receptors. In particular, it has been recognized that serotonin plays a role in various types of pathological conditions such as anxiety, depression, aggressivness, schizophrenia, suicidal behaviour, panic and autism (Zifa & Fillion, 1992).

On the basis of the binding data available for different agonists and antagonists, it has been postulated that there are several different subtypes of serotonin receptors localized in brain and peripheral tissues, and Bradley *et al.* (1987) have distinguished not less than three main classes of 5-HT receptors: 5-HT_1, 5-HT_2 and 5-HT_3. In particular, 5-HT_{1A} and 5-HT_{1B} receptor subtypes have been well characterized by radioligand binding assays by Pazos & Palacios (1985). The former selectively binds the agonist 8-OH-DPAT [8-hydroxy-2-(di-*n*-propylamino)tetralin (Middlemiss & Sozard, 1983)] and it is generally accepted that these receptors are involved in psychiatric disorders such as depression (Fuller & Robertson, 1991) and anxiety (Barrett & Vanover, 1993). Although three 5-HT_2 receptor subtypes have been proposed, only one (5-HT_{2A}) has been well typified by its pharmacological profile, that is by the specific binding of the antagonist ketanserin {3-[2-[4-(4-fluorobenzoyl)-1-piperdinyl]ethyl]-2,4(1H,3H)-quinazolinedione (Leysen, Niemegeers, Van Nueten & Laudron, 1982)}. 5-HT_2 receptor antagonists have been used with success in the clinical management of anxiety (Ceulemans, Hoppenbrouwers, Gelders & Reyntjens, 1985) and schizophrenia (Gelders, 1989). While 5-HT_1 and 5-HT_2 receptors are known to produce a modification of the level of a second messanger, *e.g.* c-AMP (adenosine monophosphate, cyclic) and IP_3 (phosphoinositide), respectively, 5-HT_3 is a neuronal receptor directly coupled with an ion channel permeant to Na^+, K^+, Ca^{2+} and other cations (Peters, Malone & Lambert, 1992) which is selectively blocked by the antagonist MDL 72222 (Boess & Martin, 1994). Antagonists at the

5-HT_3 receptor are putatively useful in the treatment of brain disorders, including those produced by drug and alcohol abuse (Kilpatrick, Brunce & Tyers, 1990; Carboni, Acquas, Leone, Perezzani & Di Chiara, 1988).

These findings have stimulated research on pharmacological agents capable of selective interaction with 5-HT receptor subtypes. Hibert, McDermott, Middlemiss, Mir & Fozard (1989) suggested that the structural features defining the 5-HT_{1A} receptor pharmacophore include an aromatic ring and a strongly basic N atom. Schmidt & Peroutka (1989) proposed a model of the 5-HT_3 receptor pharmacophore using three-dimensional computer analysis of a number of compounds of high affinity and selectivity. Several recent structural analyses of 5-HT_3 antagonists have been found to agree with the model and point to three main pharmacophoric elements: an aromatic ring, a carbonyl, or analogous function, and a basic N atom (Gozlan & Langlois, 1992).

In the present paper the crystal structures of a 5-HT_1 receptor antagonist, NAN-190.HBr, a 5-HT_3 agonist, 1-phenylbiguanide, a 5-HT_3 antagonist, MDL 72222, and a non-selective 5-HT agent, mianserin.HCl, are reported and compared with those found in the recent literature, with the aim of confirming previous hypotheses on the common stereochemical vector responsible for the serotoninergic activity and, possibly, to find the factors determining the selectivity for 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

2. Experimental

The four compounds were purchased from Research Biochemical International (RBI), Amersham Italia S.r.l., Milan, Italy. Crystal data, data collection and refinement details are given in Table 1.* All intensities were corrected for Lorentz and polarization effects. Only the intensities of compound (1), NAN-190.HBr, were corrected for absorption effects, using the scan method. The structures were solved by direct methods using the *SIR*88 (Burla *et al.*, 1989) system of programs and all other calculations were accomplished using *MolEN* (Fair, 1990) and *PARST* (Nardelli, 1983). All molecules were refined by full-matrix least-squares. The refinements were carried out on F with anisotropic non-H atoms and isotropic H atoms. All H-atom positions were determined from the F syntheses calculated after the first cycles of the isotropic refinement.

3. Description of the structures

Final coordinates are given in Table 2 and a selection of bond distances, bond angles and torsion angles in Table 3. *ORTEP*II (Johnson, 1976) views of the four compounds are shown in Figs. 1–4.

In compound (1), NAN-190.HBr, the piperazine ring adopts a chair conformation with puckering parameters (Cremer & Pople, 1975) of Q = 0.579 (3) Å, φ = −177 (3)°, θ = 4.8 (3)°. The protonated N2 atom displays a C—N2—C average angle of 111 (1)° and an average C—N2 distance of 1.498 (3) Å, while the other sp^3 hybridized N3 atom bonded to a Csp^2 atom shows a smaller degree of pyramidalization [C—N3—C average angle 113 (3)°] and a shorter C17—N3 distance, 1.417 (4) Å. These data indicate a small degree of π-conjugation along the Nsp^3—Csp^2 bond (for reference, Csp^2—Nsp^3 = 1.44 and C=N = 1.27 Å), in agreement with the observed values of the rotation angle τ around the C—N bond and of the degree of pyramidalization χ_N (Gilli, Bertolasi, Bellucci & Ferretti, 1986; Ferretti, Bertolasi, Gilli & Gilli, 1993). The actual values of τ and χ_N of 40.1 (2) and 51.8 (4)°, respectively, correspond to a medium rotation angle coupled with a high degree of pyramidalization of the nitrogen. τ and χ_N are defined as: $\tau = |\omega 1 + \omega 2|/2 = |(\pi - \omega 3) + (\pi - \omega 4)|/2$ ($0 \le \tau \le 90°$) and $\chi_N = \omega 2 - \omega 3 + \pi (\mathrm{mod}\ 2\pi) = -\omega 1 + \omega 4 + \pi (\mathrm{mod}\ 2\pi)$ [$0 \le \chi_N \le 60°$ (Dunitz & Winkler, 1975)], the torsion angles $\omega 1$, $\omega 2$, $\omega 3$ and $\omega 4$ being defined in Table 3. The phthalimido moiety is almost planar [$\Sigma(\Delta/\sigma)^2$ = 24.2] and forms with the plane of the phenyl group a dihedral angle of 2.59 (9)°. The Br^- ion is hydrogen bonded to the N2 protonated nitrogen and to the water molecule O1w with distances Br···N2 = 3.228 (3) and Br···O1w = 3.367 (2) Å.

The asymmetric unit of 1-phenylbiguanide (2) consists of four independent molecules in slightly different conformations displaying a tautomeric form, which allows the formation of a strong intramolecular N—H···N hydrogen bond [N···N average distance 2.66 (4) Å (Table 4)]. Since the two hydrogen-bonded nitrogens are at the ends of the —N=C—N=C—NH_2 heterodienic conjugated system which is formally equivalent to the β-diketone enol O=C—C=C—OH (Bertolasi, Gilli, Ferretti & Gilli, 1991) and keto-hydrazone O=C—C=N—NH (Bertolasi *et al.*, 1993) groups, the shortening of the N—H···N bonds can be imputed to an enhancement of hydrogen bond strength assisted by resonance. The crystal packing is mainly determined by a number of intermolecular N—H···N hydrogen bonds which are always resonance-assisted and imply one amine function and an imino C—N=C group. Both intra- and intermolecular interactions cooperate to produce an almost total π-delocalization along the C—N bonds of the biguanide fragment. The conformations of the three independent molecules A, B and C are similar, the biguanide group being rotated with respect to the phenyl group by angles τ_1 = 58.8 (5), 62.0 (6) and 56.2 (6)°, respectively, while in molecule D the rotation is rather different with a τ_1 value of 85.0 (6)° (the angle τ_1 is defined as: $\tau_1 = |\omega 1 + \omega 2 \pm$

* Lists of atomic coordinates, anisotropic displacement parameters, complete geometry and structure factors have been deposited with the IUCr (Reference: NA0073). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Experimental details*

	(1)	(2)	(3)	(4)
Crystal data				
Chemical formula	$C_{23}H_{28}N_3O_3^+.Br^-.1/2H_2O$	$C_8H_{11}N_5$	$C_{15}H_{17}Cl_2NO_2$	$C_{18}H_{21}N_2^+.Cl^-$
Chemical formula weight	483.42	177.21	314.21	300.83
Cell setting	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	$C2/c$	$P2_1/c$	$P\bar{1}$	$P2_1/a$
a (Å)	21.916 (4)	9.781 (2)	8.480 (3)	9.014 (2)
b (Å)	15.207 (2)	35.040 (5)	9.840 (3)	14.917 (2)
c (Å)	14.052 (2)	11.000 (2)	10.158 (4)	12.412 (2)
α (°)	90.00 (0)	90.00 (0)	90.04 (3)	90.00 (0)
β (°)	101.56 (1)	97.72 (1)	111.77 (3)	108.84 (1)
γ (°)	90.00 (0)	90.00 (0)	105.07 (3)	90.00 (0)
V (Å^3)	4588 (1)	3736 (1)	755.6 (5)	1579.5 (5)
Z	8	16	2	4
D_x (Mg m^{-3})	1.40	1.26	1.38	1.26
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71069	0.71069	0.71069	0.71069
No. of reflections for cell parameters	25	25	25	25
θ range (°)	10–15	10–15	10–15	10–15
μ (mm^{-1})	1.823	0.0843	0.430	0.237
Temperature (K)	295	295	295	295
Crystal form	Prismatic	Prismatic	Prismatic	Prismatic
Crystal size (mm)	0.52 × 0.33 × 0.17	0.48 × 0.31 × 0.21	0.48 × 0.36 × 0.19	0.47 × 0.19 × 0.07
Crystal colour	Colourless	Colourless	Colourless	Colourless
Data collection				
Diffractometer	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4
Data collection method	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
Absorption correction	ψ scan	None	None	None
T_{min}	0.75	–	–	–
T_{max}	0.992	–	–	–
No. of measured reflections	5765	9490	3478	3655
No. of independent reflections	5540	8990	3287	3437
No. of observed reflections	2617	3407	1685	1493
Criterion for observed reflections	$I > 3\sigma(I)$	$I > 2\sigma(I)$	$I > 3\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.016	0.033	0.018	0.024
θ_{max} (°)	28	28	27	27
Range of h, k, l	$-29 \rightarrow h \rightarrow 29$	$0 \rightarrow h \rightarrow 12$	$-10 \rightarrow h \rightarrow 10$	$0 \rightarrow h \rightarrow 11$
	$0 \rightarrow k \rightarrow 20$	$0 \rightarrow k \rightarrow 46$	$-12 \rightarrow k \rightarrow 12$	$0 \rightarrow k \rightarrow 19$
	$0 \rightarrow l \rightarrow 18$	$-14 \rightarrow l \rightarrow 14$	$0 \rightarrow l \rightarrow 13$	$-15 \rightarrow l \rightarrow 15$
No. of standard reflections	3	3	3	3
Frequency of standard reflections	120	120	120	120
Refinement				
Refinement on	F	F	F	F
R	0.035	0.070	0.070	0.063
wR	0.036	0.073	0.082	0.051
S	1.37	1.63	1.73	1.61
No. of reflections used in refinement	2617	3407	1685	1493
No. of parameters used	392	645	249	274
H-atom treatment	All H-atom parameters refined	All H-atom parameters refined	All H-atom parameters refined	All H-atom parameters refined
Weighting scheme	$w = 4F^2/[\sigma^2(F_o^2) + (0.03F_o^2)^2]$	$w = 4F^2/[\sigma^2(F_o^2) + (0.05F_o^2)^2]$	$w = 4F^2/[\sigma^2(F_o^2) + (0.07F_o^2)^2]$	$w = 4F^2/[\sigma(F_o^2) + (0.02F_o^2)^2]$
$(\Delta/\sigma)_{max}$	0.01	0.03	0.03	0.04
$\Delta\rho_{max}$ (e Å^{-3})	0.15	0.28	0.65	0.30
$\Delta\rho_{min}$ (e Å^{-3})	−0.18	−0.30	−0.50	−0.25
Extinction method	None	None	None	None
Source of atomic scattering factors	Cromer & Waber (1974)	Cromer & Waber (1974)	Cromer & Waber (1974)	Cromer & Waber (1974)

$\pi/2$, the torsion angles $\omega 1$ and $\omega 2$ being defined in Table 3).

Compound (3), MDL 72222, contains a planar dichlorobenzoate group linked to a tropanyl moiety. The piperidine ring N1—C3—C2—C1—C7—C6 is rotated with respect to the benzoate group by the angle τ_2 = 54.0 (3)° [τ_2 being defined by the two torsion angles $\omega 1$ and $\omega 2$ (Table 3) as: $\tau = |\omega 1 + \omega 2 + \pi/2|$ and adopts a mixed chair-envelope $^1C_4$–^1E conformation with puckering parameters Q = 0.642 (4) Å, φ = 1.7 (8) and θ = 28.5 (4)°, while the fused pyrrolidine N1—C3—C4—C5—C6 adopts an envelope ^1E conformation with puckering parameters Q = 0.440 (4) Å and φ = 1.4 (8)°. The C1—O1 bond is

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
(1) NAN-190.HBr				
Br	0.07510 (1)	0.08432 (3)	0.62029 (2)	0.0629 (1)
O1	0.0258 (1)	0.3067 (1)	0.1377 (2)	0.0586 (8)
O2	0.1944 (1)	0.4185 (2)	0.0353 (2)	0.0669 (7)
O3	0.26384 (9)	−0.2258 (1)	−0.2232 (2)	0.0564 (7)
N1	0.1152 (1)	0.3419 (2)	0.0839 (2)	0.0424 (8)
N2	0.11769 (9)	−0.0391 (2)	−0.0812 (2)	0.0356 (7)
N3	0.1585 (1)	−0.2001 (2)	−0.1566 (2)	0.0378 (7)
C1	0.0601 (1)	0.3611 (2)	0.1140 (2)	0.0425 (8)
C2	0.1459 (1)	0.4180 (2)	0.0635 (2)	0.0464 (8)
C3	0.1062 (1)	0.4919 (2)	0.0823 (2)	0.0431 (9)
C4	0.0545 (1)	0.4579 (2)	0.1117 (2)	0.0415 (7)
C5	0.0094 (2)	0.5119 (2)	0.1340 (2)	0.0551 (11)
C6	0.0166 (2)	0.6008 (2)	0.1268 (3)	0.0676 (15)
C7	0.0674 (2)	0.6355 (2)	0.0976 (3)	0.0692 (15)
C8	0.1135 (2)	0.5812 (2)	0.0749 (2)	0.0587 (13)
C9	0.1392 (1)	0.2532 (2)	0.0789 (2)	0.0509 (11)
C10	0.1068 (1)	0.2015 (2)	−0.0078 (2)	0.0456 (8)
C11	0.1352 (1)	0.1111 (2)	−0.0094 (2)	0.0460 (8)
C12	0.0997 (1)	0.0559 (2)	−0.0906 (2)	0.0424 (8)
C13	0.1844 (1)	−0.0554 (2)	−0.0857 (2)	0.0444 (8)
C14	0.1990 (1)	−0.1519 (2)	−0.0789 (2)	0.0471 (7)
C15	0.0938 (1)	−0.1892 (2)	−0.1465 (2)	0.0426 (8)
C16	0.0759 (1)	−0.0942 (2)	−0.1559 (2)	0.0432 (11)
C17	0.1786 (1)	−0.2872 (2)	−0.1686 (2)	0.0393 (8)
C18	0.2340 (1)	−0.3002 (2)	−0.2023 (2)	0.0441 (8)
C19	0.2552 (1)	−0.3846 (2)	−0.2129 (2)	0.0571 (14)
C20	0.2210 (2)	−0.4566 (2)	−0.1949 (3)	0.0607 (16)
C21	0.1660 (2)	−0.4456 (2)	−0.1659 (3)	0.0572 (15)
C22	0.1449 (1)	−0.3613 (2)	−0.1525 (2)	0.0509 (11)
C23	0.3114 (2)	−0.2354 (3)	−0.2786 (3)	0.0675 (13)
O1w	1/2	0.2825 (2)	1/4	0.0909 (16)
(2) 1-Phenylbiguanide				
N1*A*	0.9033 (4)	−0.03694 (9)	0.6322 (3)	0.0428 (15)
N2*A*	0.7235 (5)	−0.0175 (1)	0.4839 (4)	0.0854 (15)
N3*A*	0.7846 (3)	0.0212 (1)	0.6459 (3)	0.0404 (12)
N4*A*	1.0118 (4)	0.0261 (1)	0.7519 (4)	0.0544 (14)
N5*A*	0.8430 (4)	0.0689 (1)	0.7810 (3)	0.0515 (15)
C1*A*	0.8109 (4)	−0.0126 (1)	0.5893 (4)	0.0436 (15)
C2*A*	0.8821 (4)	0.0381 (1)	0.7251 (4)	0.0380 (15)
C3*A*	0.9129 (4)	−0.0726 (1)	0.5738 (4)	0.0447 (15)
C4*A*	1.0337 (5)	−0.0839 (1)	0.5355 (4)	0.0544 (16)
C5*A*	1.0503 (5)	−0.1195 (2)	0.4885 (5)	0.0730 (22)
C6*A*	0.9479 (6)	−0.1446 (2)	0.4771 (6)	0.0954 (24)
C7*A*	0.8254 (7)	−0.1347 (2)	0.5118 (8)	0.1331 (33)
C8*A*	0.8085 (6)	−0.0988 (2)	0.5616 (7)	0.1057 (27)
N1*B*	0.5904 (4)	0.0709 (1)	0.2104 (3)	0.0520 (15)
N2*B*	0.7250 (4)	0.0650 (1)	0.0521 (4)	0.0722 (15)
N3*B*	0.6620 (4)	0.0107 (1)	0.1433 (3)	0.0497 (15)
N4*B*	0.4844 (4)	0.0048 (1)	0.2673 (4)	0.0539 (15)
N5*B*	0.5948 (4)	−0.0474 (1)	0.2027 (4)	0.0584 (15)
C1*B*	0.6572 (5)	0.0497 (1)	0.1418 (4)	0.0468 (15)
C2*B*	0.5781 (4)	−0.0096 (1)	0.2040 (4)	0.0444 (15)
C3*B*	0.5897 (5)	0.1111 (1)	0.1984 (4)	0.0512 (13)
C4*B*	0.7069 (6)	0.1330 (2)	0.2240 (5)	0.0704 (21)
C5*B*	0.6984 (8)	0.1723 (2)	0.2208 (6)	0.1076 (28)
C6*B*	0.5764 (9)	0.1902 (2)	0.1915 (6)	0.1129 (32)
C7*B*	0.4612 (7)	0.1691 (2)	0.1661 (5)	0.0966 (25)
C8*B*	0.4646 (6)	0.1296 (2)	0.1687 (5)	0.0683 (19)
N1*C*	0.4967 (4)	0.1745 (1)	0.7030 (3)	0.0494 (15)
N2*C*	0.5468 (4)	0.1330 (1)	0.8711 (3)	0.0547 (15)
N3*C*	0.5774 (4)	0.1115 (1)	0.6825 (3)	0.0425 (13)
N4*C*	0.5400 (4)	0.1445 (1)	0.4947 (3)	0.0630 (15)
N5*C*	0.6031 (4)	0.0816 (1)	0.5028 (3)	0.0512 (15)
C1*C*	0.5408 (4)	0.1423 (1)	0.7494 (4)	0.0410 (15)
C2*C*	0.5723 (4)	0.1135 (1)	0.5613 (4)	0.0416 (16)
C3*C*	0.4537 (5)	0.2037 (1)	0.7768 (4)	0.0482 (14)
C4*C*	0.5358 (6)	0.2202 (1)	0.8757 (5)	0.0623 (18)
C5*C*	0.4868 (7)	0.2498 (2)	0.9412 (5)	0.0805 (25)
C6*C*	0.3591 (7)	0.2634 (2)	0.9086 (5)	0.0859 (24)
C7*C*	0.2735 (6)	0.2479 (2)	0.8102 (5)	0.0778 (23)
C8*C*	0.3233 (5)	0.2187 (1)	0.7462 (5)	0.0608 (18)
N1*D*	0.9783 (4)	−0.1296 (1)	1.0414 (4)	0.0641 (15)
N2*D*	0.7876 (4)	−0.1373 (1)	1.1402 (5)	0.1009 (19)
N3*D*	0.8214 (4)	−0.0795 (1)	1.0598 (3)	0.0449 (14)
N4*D*	0.9206 (5)	−0.0729 (1)	0.8773 (4)	0.0796 (18)
N5*D*	0.7969 (4)	−0.0250 (1)	0.9475 (4)	0.0642 (15)
C1*D*	0.8675 (4)	−0.1166 (1)	1.0771 (4)	0.0468 (15)
C2*D*	0.8488 (5)	−0.0604 (1)	0.9618 (4)	0.0466 (15)
C3*D*	1.0136 (5)	−0.1686 (1)	1.0622 (5)	0.0591 (14)
C4*D*	1.0864 (6)	−0.1810 (2)	1.1706 (5)	0.0728 (23)
C5*D*	1.1236 (6)	−0.2187 (2)	1.1860 (6)	0.0953 (21)
C6*D*	1.0886 (7)	−0.2448 (2)	1.0940 (7)	0.1034 (29)
C7*D*	1.0167 (7)	−0.2329 (2)	0.9881 (7)	0.1014 (27)
C8*D*	0.9785 (6)	−0.1952 (2)	0.9711 (6)	0.0859 (24)
(3) MDL 72222				
Cl1	0.2957 (2)	0.0033 (2)	0.2156 (2)	0.0743 (5)
Cl2	−0.3122 (1)	0.1203 (2)	0.1450 (2)	0.0566 (5)
O1	0.4011 (3)	0.5440 (3)	0.1813 (3)	0.0389 (9)
O2	0.1582 (4)	0.6030 (4)	0.1714 (4)	0.0618 (12)
N1	0.8721 (5)	0.7892 (4)	0.3573 (4)	0.0440 (15)
C1	0.4975 (5)	0.6952 (4)	0.1896 (5)	0.0368 (13)
C2	0.5749 (6)	0.7625 (5)	0.3414 (6)	0.0492 (17)
C3	0.7500 (6)	0.7355 (5)	0.4293 (5)	0.0475 (18)
C4	0.7381 (6)	0.5781 (6)	0.4365 (5)	0.0479 (19)
C5	0.7781 (6)	0.5370 (5)	0.3092 (6)	0.0523 (21)
C6	0.8060 (5)	0.6763 (5)	0.2404 (5)	0.0406 (15)
C7	0.6371 (6)	0.6945 (5)	0.1309 (5)	0.0399 (20)
C8	1.0576 (7)	0.8083 (7)	0.4523 (7)	0.0666 (25)
C9	0.2349 (5)	0.5163 (5)	0.1739 (5)	0.0391 (16)
C10	0.1567 (5)	0.3607 (5)	0.1721 (5)	0.0346 (15)
C11	0.2540 (5)	0.2650 (5)	0.1899 (5)	0.0388 (16)
C12	0.1743 (6)	0.1239 (5)	0.1932 (5)	0.0431 (19)
C13	0.0003 (5)	0.0778 (5)	0.1791 (5)	0.0425 (16)
C14	−0.0938 (5)	0.1749 (5)	0.1602 (5)	0.0391 (15)
C15	−0.0190 (5)	0.3165 (5)	0.1551 (5)	0.0391 (16)
(4) Mianserin.HCl				
Cl	0.2165 (1)	0.6074 (1)	0.6211 (1)	0.0640 (5)
N1	0.0896 (4)	0.4373 (2)	0.8773 (3)	0.0317 (11)
N2	−0.0637 (4)	0.5412 (3)	0.6773 (3)	0.0369 (11)
C1	0.0755 (4)	0.4008 (3)	0.7644 (3)	0.0310 (15)
C2	0.0637 (5)	0.2994 (3)	0.7480 (3)	0.0344 (16)
C3	0.0174 (5)	0.2401 (3)	0.8185 (4)	0.0342 (16)
C4	−0.0004 (5)	0.2699 (3)	0.9296 (4)	0.0405 (16)
C5	0.2399 (5)	0.2714 (3)	1.1063 (4)	0.0436 (16)
C6	0.3738 (5)	0.3128 (3)	1.1753 (4)	0.0488 (18)
C7	0.4195 (5)	0.3943 (4)	1.1446 (4)	0.0463 (21)
C8	0.3299 (5)	0.4341 (3)	1.0453 (4)	0.0405 (15)
C9	0.1929 (4)	0.3937 (3)	0.9747 (3)	0.0340 (17)
C10	0.1476 (5)	0.3111 (3)	1.0057 (3)	0.0342 (16)
C11	0.1037 (5)	0.5350 (3)	0.8750 (4)	0.0403 (16)
C12	−0.0385 (5)	0.5757 (3)	0.7931 (4)	0.0411 (16)
C13	−0.2057 (6)	0.5817 (4)	0.5928 (4)	0.0566 (17)
C14	−0.0692 (5)	0.4421 (3)	0.6790 (4)	0.0408 (17)
C15	0.0871 (5)	0.2670 (3)	0.6502 (4)	0.0423 (16)
C16	0.0611 (6)	0.1776 (4)	0.6187 (4)	0.0506 (16)
C17	0.0154 (6)	0.1189 (3)	0.6868 (4)	0.0507 (17)
C18	−0.0035 (5)	0.1502 (3)	0.7860 (4)	0.0449 (15)

in an axial position, giving rise to the *endo* configuration of the tropanyl moiety.

Compound (4), mianserin.HCl, contains a piperazine bonded to a phenyl ring as in compound (1); the two rings are, however, fused through an azepino group. The rotation of piperazine with respect to the phenyl (C5–C10) and the pyramidalization of its N1 atom can be defined by means of the usual parameters τ = 46.2 (5)° and χ_N = 47.5 (5)°; the distance 1.423 (5) Å is shorter

Table 3. *Selected bond distances (Å), bond angles (°) and torsion angles (°)*

(1) NAN-190.HBr

N1—C1	1.388 (4)	N2—C13	1.497 (3)
N1—C2	1.397 (4)	N2—C16	1.503 (4)
N1—C9	1.455 (4)	N3—C14	1.459 (4)
C1—O1	1.209 (4)	N3—C15	1.462 (3)
C2—O2	1.207 (4)	N3—C17	1.417 (4)
N2—C12	1.496 (4)		
C1—N1—C2	111.9 (2)	C13—N2—C16	110.0 (2)
C1—N1—C9	123.7 (2)	C14—N3—C15	109.1 (2)
C2—N1—C9	124.4 (3)	C14—N3—C17	113.7 (3)
C12—N2—C13	113.5 (2)	C15—N3—C17	116.6 (2)
C12—N2—C16	111.3 (3)		
C1—N1—C9—C10	77.3 (3)	C14—N3—C17—C18	−67.4 (3) ω1
C2—N1—C9—C10	−105.8 (3)	C15—N3—C17—C22	−12.9 (4) ω2
C11—C12—N2—C13	−62.5 (3)	C14—N3—C17—C22	115.4 (3) ω3
C11—C12—N2—C16	172.7 (2)	C15—N3—C17—C18	164.2 (2) ω4

(2) 1-Phenylbiguanide

	A	*B*	*C*	*D*
N1—C3	1.414 (5)	1.415 (5)	1.405 (6)	1.420 (5)
N1—C1	1.285 (5)	1.296 (6)	1.289 (5)	1.285 (6)
N2—C1	1.356 (6)	1.370 (6)	1.371 (6)	1.328 (6)
N3—C1	1.378 (5)	1.367 (5)	1.380 (5)	1.381 (5)
N3—C2	1.340 (5)	1.331 (6)	1.329 (6)	1.326 (6)
N4—C2	1.331 (5)	1.323 (6)	1.324 (5)	1.313 (7)
N5—C2	1.324 (5)	1.335 (5)	1.344 (5)	1.342 (5)
C3—N1—C1	120.4 (3)	120.8 (3)	121.3 (3)	119.2 (4)
N1—C1—N2	124.2 (4)	121.7 (4)	124.2 (4)	123.1 (4)
N1—C1—N3	124.7 (3)	125.8 (4)	124.8 (4)	124.4 (4)
N2—C1—N3	111.1 (4)	112.4 (3)	110.8 (4)	112.5 (4)
C1—N3—C2	120.9 (4)	121.2 (3)	121.1 (4)	119.3 (3)
N3—C2—N4	125.3 (4)	125.3 (4)	124.9 (4)	126.3 (4)
N3—C2—N5	115.9 (4)	116.1 (3)	117.1 (4)	116.6 (4)
N4—C2—N5	118.7 (4)	118.6 (4)	118.0 (3)	117.1 (4)
C4—C3—N1—C1	124.1 (4)	−64.5 (6)	58.3 (6)	−86.0 (6) ω1
C8—C3—N1—C1	−61.6 (6)	120.6 (5)	−125.2 (5)	96.0 (6) ω2
C3—N1—C1—N3	173.4 (4)	−178.2 (4)	176.1 (4)	−178.7 (4)
N1—C1—N3—C2	24.6 (6)	11.0 (7)	1.6 (6)	31.0 (7)
C1—N3—C2—N4	3.9 (6)	0.0 (7)	3.6 (6)	−1.8 (7)

(3) MDL 72222

N1—C8	1.470 (6)	C9—O1	1.337 (5)
N1—C3	1.471 (7)	C9—O2	1.195 (7)
N1—C6	1.463 (6)	C9—C10	1.499 (6)
C1—O1	1.485 (5)		
C3—N1—C6	100.2 (4)	C1—O1—C9	116.8 (3)
C3—N1—C8	112.0 (4)	O1—C9—O2	125.2 (5)
C6—N1—C8	113.6 (4)	O1—C9—C10	111.0 (4)
O1—C1—C2	110.1 (4)	O2—C9—C10	123.8 (5)
O1—C1—C7	105.4 (3)		
C8—N1—C3—C2	162.7 (4)	C7—C1—O1—C9	−155.1 (4) ω2
C8—N1—C3—C4	−76.2 (5)	C1—O1—C9—C10	−177.7 (4)
C8—N1—C6—C5	74.5 (5)	O1—C9—C10—C11	5.7 (6)
C8—N1—C6—C7	−164.5 (4)	O1—C9—C10—C15	−175.8 (4)
C2—C1—O1—C9	83.1 (5) ω1		

(4) Mianserin.HCl

N1—C1	1.470 (5)	N2—C12	1.474 (6)
N1—C9	1.423 (5)	N2—C13	1.495 (6)
N1—C11	1.464 (5)	N2—C14	1.480 (6)
C1—N1—C9	118.2 (3)	C13—N2—C14	112.9 (4)
C1—N1—C11	109.4 (3)	N1—C1—C2	118.4 (3)
C9—N1—C11	115.7 (3)	C1—C2—C3	124.4 (4)
C12—N2—C13	111.7 (4)	C2—C3—C4	121.8 (4)
C12—N2—C14	109.3 (4)	C3—C4—C10	111.3 (4)

Table 3 (*cont.*)

C1—N1—C9—C10	−72.9 (5) ω1, $T_{1'}$	N1—C9—C10—C4	4.8 (6) T_0
C11—N1—C9—C8	−19.6 (6) ω2	C3—C4—C10—C9	69.3 (5) T_1
C1—N1—C9—C8	112.9 (4) ω3	C2—C3—C4—C10	−56.1 (6) T_2
C11—N1—C9—C10	154.6 (4) ω4	C1—C2—C3—C4	−10.2 (7) T_3
C9—N1—C1—C14	165.4 (4)	N1—C1—C2—C3	20.6 (6) $T_{3'}$
C9—N1—C1—C12	−161.3 (4)	C9—N1—C1—C2	43.1 (5) $T_{2'}$

Table 4. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
(1) NAN-190.HBr				
N2—H2N···Br^{i}	0.88 (3)	2.36 (3)	3.228 (3)	167 (3)
O1*w*—H1*w*···Br^{ii}	0.84 (4)	2.53 (4)	3.367 (2)	174 (3)
(2) 1-Phenylbiguanide				
N2*A*—H21*A*···N5*B*^{iii}	0.76 (4)	2.86 (3)	3.347 (6)	125 (3)
N2*A*—H22*A*···N4*B*^{iii}	0.92 (4)	2.52 (5)	3.203 (6)	132 (4)
N4*A*—H41*A*···N1*A*^{iii}	0.82 (4)	2.12 (4)	2.714 (5)	128 (3)
N5*A*—H52*A*···N3*C*^{iii}	0.87 (4)	2.22 (4)	3.065 (5)	163 (4)
N4*B*—H41*B*···N1*B*^{iii}	0.89 (4)	1.95 (4)	2.647 (5)	134 (3)
N4*C*—H41*C*···N1*C*^{iii}	0.93 (4)	1.90 (3)	2.607 (5)	131 (3)
N5*C*—H51*C*···N1*B*^{iii}	0.90 (6)	2.39 (5)	3.224 (5)	153 (5)
N5*C*—H52*C*···N3*A*^{iii}	0.84 (3)	2.24 (4)	3.059 (5)	166 (3)
N4*D*—H41*D*···N1*D*^{iii}	0.88 (4)	2.13 (3)	2.693 (5)	121 (3)
N4*D*—H42*D*···N1*A*	0.90 (4)	2.07 (4)	2.960 (5)	169 (4)
N5*D*—H51*D*···N3*A*	0.85 (4)	2.86 (4)	3.679 (5)	161 (4)
N5*D*—H51*D*···N4*A*	0.85 (4)	2.91 (5)	3.670 (6)	150 (4)
N4*A*—H42*A*···N3*D*^{iv}	1.04 (4)	2.08 (5)	3.090 (5)	163 (4)
N5*A*—H51*A*···N1*D*^{iv}	0.79 (3)	2.48 (3)	3.237 (5)	161 (3)
N5*B*—H52*B*···N3*D*^{v}	0.88 (4)	2.21 (4)	3.096 (6)	176 (4)
N4*B*—H42*B*···N3*A*^{vi}	0.80 (3)	2.31 (3)	3.056 (5)	156 (3)
N5*B*—H51*B*···N3*C*^{vi}	0.80 (3)	2.41 (3)	3.170 (5)	161 (3)
N2*C*—H22*C*···N2*B*^{vii}	0.90 (4)	2.61 (3)	3.427 (5)	151 (3)
N5*D*—H52*D*···N3*B*^{vii}	0.92 (4)	2.07 (4)	2.951 (6)	162 (4)
N2*D*—H22*D*···N2*C*^{viii}	0.85 (5)	2.48 (5)	3.260 (6)	152 (4)
(4) Mianserin.HCl				
N2—H2···Cl	1.04 (5)	1.96 (5)	2.996 (4)	175 (4)

Symmetry codes: (i) $x, -y, z - \frac{1}{2}$; (ii) $\frac{1}{2} - x, \frac{1}{2} - y, 1 - z$; (iii) x, y, z; (iv) $2 - x, -y, 2 - z$; (v) $x, y, z - 1$; (vi) $1 - x, -y, 1 - z$; (vii) $x, y, z + 1$; (viii) $1 - x, -y, 2 - z$.

than the mean pure single Csp^2—Nsp^3 bond of 1.44 Å (Ferretti, Bertolasi, Gilli & Gilli, 1993) and indicates some conjugation along the N1—C9 bond. The piperazine is in a chair conformation with the puckering parameters Q = 0.584 (4) Å, φ = −4 (7)° and θ = 176 (4)°. The seven-membered azepino ring assumes an approximate boat conformation with total puckering parameter Q_T = 0.930 (4) Å (Cremer & Pople, 1975) and asymmetry parameter (Duax, Weeks & Rohrer, 1976) ΔC_s(C2) = $\{[T_0^2 + \Sigma_{i=1}^{3}(T_i + T_{i'})^2]/4\}^{1/2}$ = 8.85°, indicating a small deviation from the ideal geometry. The ring conformation can also be described (Gilli, Borea, Bertolasi & Sacerdoti, 1982) by the angles among the mean planes *P*1 = N1—C9—C10—C4, *P*2 = N1—C1—C3—C4 and *P*3 = C1—C2—C3, the stern (*P*1 − *P*2) and bow (*P*2 − *P*3) angles assuming values of 58.7 (2) and 14.6 (3)°, respectively. The angle between the two phenyl rings is 62.9 (1)°. The chlorine ion is linked by a hydrogen bond to the protonated N2 atom with N2—Cl 2.996 (4) Å (Table 4).

3.1. *Pharmacological implications*

The endogenous ligand 5-HT (serotonin) contains a planar hydroxyindole group and a flexible ethylamino chain (see scheme of Table 5). The pharmacological studies quoted above agree in indicating that the receptor binding ability of serotonin is to be related to a hydrogen bond donated by the protonated amino group and to the capacity of the planar indole moiety to form charge-tranfer interactions with the receptor, as actually observed in the crystal structure of the serotonin picrate complex (Thewalt & Bugg, 1972), where the serotonin cation acts as a π-electron donor and the picrate anion as a π-electron acceptor. The ethylamino chain conformation strongly affects the distance between the phenyl group and the protonated nitrogen, as well as the hydrogen-bond stereochemistry, and is supposed to play an important role in determining the binding selectivity towards the different 5-HT receptor subtypes. A systematic search on the Cambridge Structural Database (Allen *et al.*, 1979) allowed us to find eight serotonin derivatives which can be thought to represent the possible stable conformations of the flexible chain. The data, reported in Table 5, show how different conformations can produce quite different distances between the two essential parts of serotonin, the phenyl ring and the aminic nitrogen, which range from 4.82 Å, for a *gg*, to 6.47 Å for a *tt* full-extended conformation. The possibility that this distance may have a relevant role in the definition of the stereochemical vector most suited to bind to each serotonin receptor subtype can be verified by comparing the crystal structures of all available 5-HT receptor ligands. An accurate analysis of the recent literature has made possible identification of 23 cases, most of which concern selective ligands

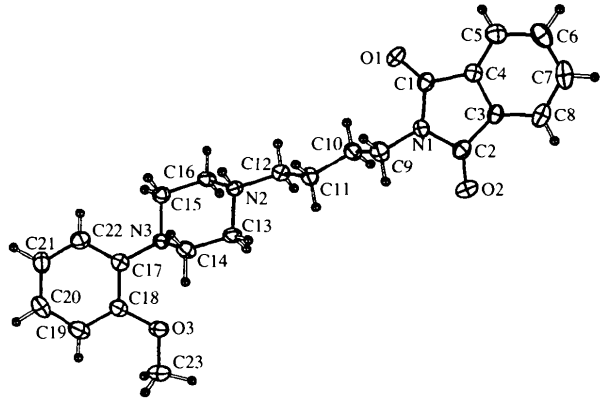


Fig. 1. *ORTEP*II (Johnson, 1976) view of the NAN-190 cation showing the thermal ellipsoids at 30% probability.

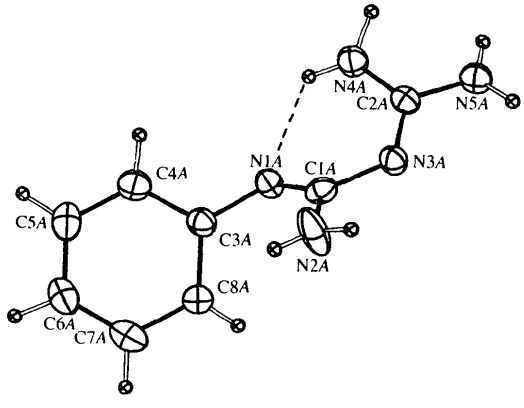


Fig. 2. *ORTEP*II (Johnson, 1976) view of molecule *A* of 1-phenylbiguanide showing the thermal ellipsoids at 30% probability.

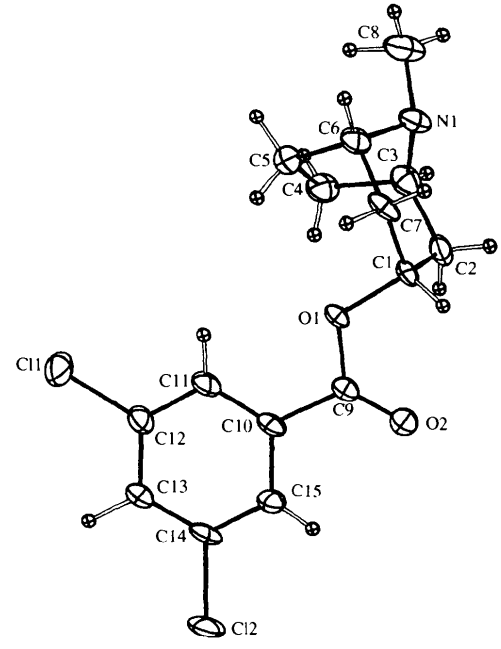


Fig. 3. *ORTEP*II (Johnson, 1976) view of MDL 72222 showing the thermal ellipsoids at 30% probability.

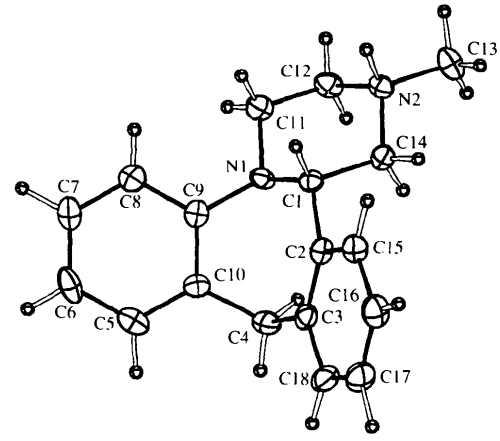


Fig. 4. *ORTEP*II (Johnson, 1976) view of the mianserin cation showing the thermal ellipsoids at 30% probability.

for 5-HT_1, 5-HT_2 and 5-HT_3 receptor subtypes. Their chemical formulae are summarized in Figs. 5, 6 and 7 and a selection of their geometrical parameters is given in Tables 6, 7 and 8.

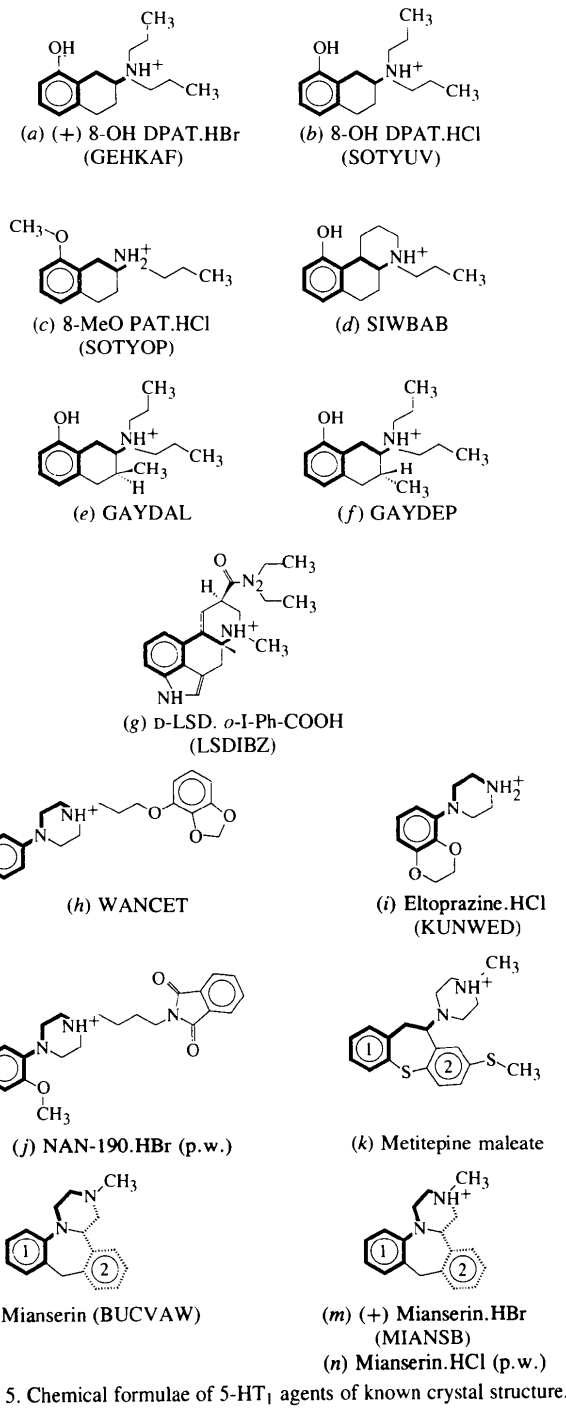


Fig. 5. Chemical formulae of 5-HT_1 agents of known crystal structure. The atoms which define the pharmacological common vector are linked by bold lines. For mianserin two vectors with similar distances can be distinguished; they are marked in two different ways: with bold lines and hatchings (p.w. = present work).

The structures of 5-HT_1 ligands (Table 6 and Fig. 5), although belonging to several different chemical classes, display definite regularities. All molecules exhibit a protonated or protonable aminic nitrogen separated by a short chain of three or four atoms from a phenyl ring, with a N—phenyl centroid distance of 5.04–5.68 Å. These distances match those found in serotonin derivatives in their *gg* or *tg* conformations (Table 5) and their constancy is obtained because of heavy geometrical constraints. At least two atoms belonging to the short chain connecting the aminic nitrogen to the phenyl are in fact embedded in a cycle, with the consequence that changes in chain conformation cannot modify the N—phenyl centroid distance, but only the N^+—H hydrogen bond direction. A general characteristic of these 5-HT_1 drugs is that the protonated nitrogens can carry substituents formed by long and bulky chains, a feature which is also found in 5-HT_2 but not in 5-HT_3 ligands. Thus, *it may be concluded that the stereochemical vector of 5-HT_1 activity consists of a protonated nitrogen, even*

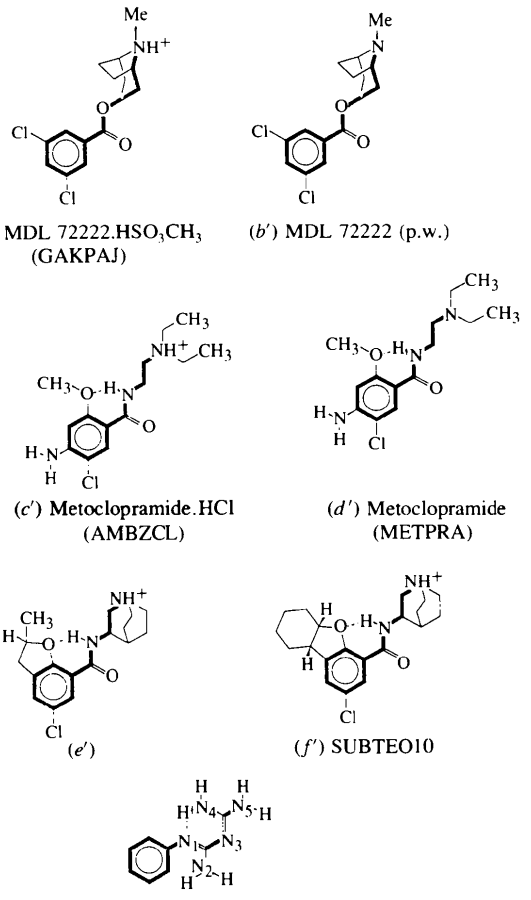
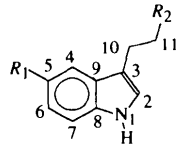


Fig. 6. Chemical formulae of 5-HT_3 agents of known crystal structure. The atoms which define the pharmacological common vector are linked by bold lines (p.w. = present work).

Table 5. *Conformational and geometrical parameters (Å, °) of 5-HT (serotonin) derivatives*



φ_1 = Torsion angle 9-3-10-11.
φ_2 = Torsion angle 3-10-11-N.
$d(C—N)$ = distance between the centroid of phenyl ring and N atom belonging to R_2 group.

	Chemical name	Refcode	R_1	R_2	φ_1	φ_2	Conf.	$d(C—N)$
(s1)	Serotonin oxalate[a]	SERHOX	OH	NH_3^+	−171.7	179.7	*tt*	6.47
(s2)	5-Methoxy-(*N,N*)-dimethyltryptamine.HCl[b]	MOTYPT	OMe	$NH(CH_3)_2^+$	161.5	−179.2	*tt*	6.47
(s3)	Serotonin.creatinine sulfate[c]	HTRCRS	OH	NH_3^+	166.7	−172.6	*tt*	6.40
(s4)	5-Hydroxy-(*N,N*)-dimethyltryptamine[d]	BUFTEN	OH	$N(CH_3)_2$	−88.8	175.3	*gt*	5.96
(s5)	5-Methoxy tryptamine.5-methoxyindole-3-acetic acid[e]	MIAMTA	OMe	NH_3^+	−168.5	70.2	*tg*	5.68
(s6)	5-Methoxy tryptamine.indole-3-acetic acid[e]	IAAMTA	OMe	NH_3^+	−74.7	−64.8	*gg*	5.20
(s7)	Serotonin picrate[f]	SERPIC	OH	NH_3^+	−67.5	−66.6	*gg*	5.10
(s8)	5-Methoxy tryptamine[g]	MXTRYP	OMe	NH_2	63.3	54.7	*gg*	4.82

(*a*) Amit, Mester, Klewe & Furberg (1978); (*b*) Falkenberg & Carlström (1971); (*c*) Karle, Dragonette & Brenner (1965); (*d*) Falkenberg (1972); (*e*) Sakaki *et al.* (1976); (*f*) Thewalt & Bugg (1972); (*g*) Quarles, Templeton & Zalkin (1976).

Table 6. *Geometrical parameters (Å) for 5-HT$_1$ agents for compounds of Fig. 5, d(C—N) = distance between the centroid of a phenyl ring and a protonated or protonable nitrogen*

Drug name	Pharmacological profile	Refcode	$d(C—N)$	$d(C—N1)$	$d(C1—N)$	$d(C2—N)$
(*a*) (+) 8-OH DPAT.HBr	Agonist	GEHKAF	5.17			
(*b*) 8-OH DPAT.HCl	Agonist	SOTYUV	5.16			
(*c*) 8-MeO PAT.HCl	Agonist	SOTYOP	5.17			
(*d*)	Agonist	SIWBAB	5.17			
(*e*)	Agonist	GAYDAL	5.22			
(*f*)	Agonist	GAYDEP	5.20			
(*g*) D-LSD.*o*-I-Ph-COOH	Agonist n.s.*	LSDIBZ		5.13		
(*h*)	Agonist	WANCET			5.68	
(*i*) Eltoprazine.HCl	Agonist	KUNWED	5.65			
(*j*) NAN-190.HBr	Antagonist	p.w.			5.66	
(*k*) Metitepine maleate	Antagonist	‡			5.15	(3.66)
					(7.68)	(6.17)
(*l*) Mianserin	Antagonist n.s.†	BUCVAW			5.66	5.06
(*m*) (+) Mianserin.HBr	Antagonist n.s.†	MIANSB			5.66	5.04
(*n*) Mianserin.HCl	Antagonist n.s.†	p.w.			5.67	5.04

p.w. = Present work. * Non-selective agonist. † Non-selective antagonist. ‡ Structure retrieved from recent literature and not yet included in the CSD files. (*a*) Karlson, Petterson, Sundell, Arvidsson & Hacksell (1988); (*b, c*) Kirby, McAlpine, Sawyer, Taylor & Blake (1992); (*d*) Mellin *et al.* (1991); (*e,f*) Mellin *et al.* (1988); (*g*) Baker, Chothia, Pauling & Weber (1972); (*h*) Okamoto, Fujii & Tomita (1993); (*i*) Verdonk, Kanters & Kroon (1992); (*j*) Present work; (*k*) Blaton, Peeters & De Ranter (1995*b*); (*l*) Van Meerssche & Declercq (1983); (*m*) Van Rij & Feil (1973); (*n*) present work.

Table 7. *Geometrical parameters (Å) for 5-HT$_3$ agents for compounds of Fig. 6, d(C—N) = distance between the centroid of a phenyl ring and a protonated or protonable nitrogen*

Drug name	Pharmacological profile	Refcode	$d(C—N)$	$d(C—N5)$
(*a'*) MDL 72222.HSO_3CH_3	Antagonist	GAKPAJ	7.35	
(*b'*) MDL 72222	Antagonist	p.w.	7.16	
(*c'*) Metoclopramide.HCl	Antagonist	AMBZCL	6.09	
(*d'*) Metoclopramide	Antagonist	METPRA	6.34	
(*e'*)	Antagonist	*	7.37	
(*f'*)	Antagonist	SUBTEO10	6.87	
(*g'*) 1-Phenylbiguanide	Agonist	p.w.		6.94

p.w. = present work. * Structure retrieved from recent literature and not yet included in the CSD files. (*a'*) Carpy, Lemrabett & Colleter (1988); (*b'*) present work; (*c'*) Blaton, Peeters, De Ranter, Denisoff & Molle (1980); (*d'*) Cesario, Pascard, El Moukhtari & Jung (1981); (*e'*) Kuroita *et al.* (1994); (*f'*) Ammon *et al.* (1993); (*g'*) present work.

alkylated by relatively long chains, having a separation of 5–6 Å from the centroid of an aromatic ring. Besides providing a great affinity for the 5-HT$_1$ receptor, this vector seems able to ensure a high 5-HT$_1$ selectivity of compounds in Fig. 5; mianserin and D-LSD being the only ones able to also bind to 5-HT$_2$ and 5-HT$_3$ receptors with some affinity.

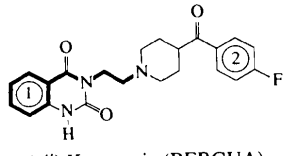
The pharmacophoric part for selective 5-HT$_3$ receptor binding seems to require three main features: an aromatic ring, a basic nitrogen and a hydrogen-bond acceptor. This latter functional group is provided by a carbonyl in almost all compounds and by an iminic nitrogen (N_3) in 1-phenylbiguanide. The basic nitrogen and the phenyl ring are separated by a chain of five or six atoms, which gives values of 6.09–7.37 Å for the N—phenyl centroid distances. In these ligands the chain conformation is not

Table 8. *Geometrical parameters (Å) for 5-HT$_2$ agents for compounds of Fig. 7, d(C—N) = distance between the centroid of a phenyl ring (or heterocycle) and a basic nitrogen*

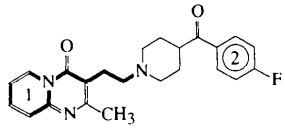
Drug name	Pharmacological profile	Refcode	*d*(C1—N)	*d*(C2—N)	*d*(C2—N1)
(*a''*) Ketanserin	Antagonist	BERGUA	7.26	6.67	
(*b''*) Pirenperone	Antagonist	*	7.19	6.72	
(*c''*) Risperidone	Antagonist	WASTEP	7.28	6.76	
(*d''*) Cinanserin.HCl	Antagonist	DIPHUF10	6.10		6.20
(*e''*) Metergoline	Antagonist	LYSDOL	7.66	5.74	

* Structure retrieved from recent literature and not yet included in the CSD files. (*a''*) Peeters, Blaton & De Ranter (1982); (*b''*) Blaton, Peeters & De Ranter (1995*a*); (*c''*) Peeters, Blaton & De Ranter (1993); (*d''*) Peeters, Blaton & De Ranter (1986); (*e''*) Foresti Serantoni, Sabatino, Riva di Sanseverino & Sheldrick (1977).

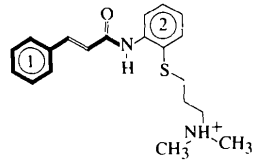
fixed by annulation (as in the previous case), but is, likewise, partially constrained by the partial double-bond character or the formation of intramolecular hydrogen bonds. MDL 72222 includes a planar benzoate fragment, while Metoclopramide and the two 2,3-dihydrobenzofuran-7-carboxamide derivatives (*e'* and *f'* in Table 7 and Fig. 6) contain an amidic group liable to form an intramolecular N—H···O bond with an oxygenated *ortho*-substituent on the phenyl ring; the biguanide group of structure (3) is kept planar and conformationally rigid by a similar intramolecular N—H···N hydrogen bond. A final important characteristic of these 5-HT$_3$ ligands is that the nitrogen does not allow, at variance with 5-HT$_1$ receptor ligands, substituents bulkier than an ethylic group.



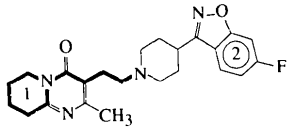
(*a''*) Ketanserin (BERGUA)



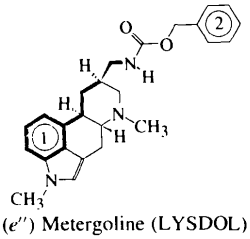
(*b''*) Pirenperone



(*d''*) Cinanserin.HCl (DIPHUF10)



(*c''*) Riperidone (WASTEP)



(*e''*) Metergoline (LYSDOL)

Fig. 7. Chemical formulae of 5-HT$_2$ agents of known crystal structure. The atoms which define the pharmacological common vector are linked by bold lines.

Also, *5-HT$_2$ receptor ligands (Fig. 7, Table 8) include the aromatic ring–basic nitrogen leit-motif, which is typical of 5-HT activity*, although, in some cases, the phenyl is replaced by a heterocyclic ring (*e.g.* in pirenperone and risperidone). The chains between the centroid of the ring (marked as 1 in Fig. 7) and the nitrogen, as in 5-HT$_3$ receptor ligands, display distances in the range 6.10–7.66 Å and some degree of conformational freedom. The factor determining the selectivity of these compounds for the 5-HT$_2$ receptor can be singled out in the systematic occurrence of very large *N*-substituents endowed with a further phenyl group (marked as 2) which could play a specific role in the binding process.

In summary, the analysis carried out on the available crystal structures of 5-HT$_1$, 5-HT$_2$ and 5-HT$_3$ selective drugs suggests that the three types of ligands can be discriminated in terms of only two factors: (i) the length of the stereochemical vector connecting the *centroid of an aromatic ring* (or a heterocycle for 5-HT$_2$ ligands) and a *basic nitrogen*, and (ii) the dimensions of the substituents at this nitrogen. Allowing the vector to assume the values of *short* and *long* and the *N*-substituent those of *small* and *large*, the selective ligands of the three receptor subtypes could be tentatively defined as: 5-HT$_1$ = *short, large*; 5-HT$_2$ = *long, large*; 5-HT$_3$ = *long, small.*

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