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Structure and Serotonin 5-HT_{2C} Receptor Activity of *ortho*- and *meta*-Substituted Phenylpiperazines

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Abstract

The structural characteristics of *ortho*- and *meta*-substituted phenylpiperazines have been investigated in order to understand their actions at the serotonin 5-HT_{2C} receptor. The crystal structures of the 4-methylated analogues of two phenylpiperazines that are already known as 5-HT_{2C} ligands, 1-(1-naphthyl)-4-methylpiperazine (1NMP) and 1-[(3-trifluoromethyl)phenyl]-4-methylpiperazine (TFMPMP), and those of two novel 5-HT_{2C} ligands, 1-(2-methoxyphenyl)piperazine (oMPP) and 1-(3-methoxyphenyl)piperazine (mMPP), are determined. Molecular mechanics calculations are performed to calculate the energy profiles of six phenylpiperazines for rotation about the central phenyl–nitrogen bond. The activities of several phenylpiperazines, in combination with their crystal structures and conformational characteristics, lead to the hypothesis that the conformation for which the piperazine ring and the phenyl ring are approximately co-planar should be the 5-HT_{2C} receptor 'activating' conformation. This hypothesis is then used to predict the activities of the two novel 5-HT_{2C} ligands oMPP and mMPP. oMPP is predicted to be an antagonist at this receptor, whereas mMPP is predicted to be an agonist. As this prediction was confirmed by *in vitro* and *in vivo* tests, the proposed conformation is very likely to be responsible for the activation of the 5-HT_{2C} receptor.

1. Introduction

In 1984 Pazos and colleagues characterized a new serotonin receptor that is very abundant in the choroid plexus (Pazos *et al.*, 1984). This receptor was classified as a 5-HT_1-type receptor, based on its neurochemical profile, and it was named the 5-HT_{1C} receptor. Later, this classification was revoked and, because of the similarity in sequence and pharmacology with the 5-$HT_{2(A)}$ receptor, the name was changed to the 5-HT_{2C} receptor (Humphry *et al.*, 1993). In 1986 Conn and colleagues discovered that the 5-HT_{2C} receptor is linked to phosphoinositide turnover in rat choroid plexus (Conn *et al.*, 1986). This second-messenger coupling was also found in pig choroid plexus (Hoyer *et al.*, 1989) and rat hippocampus (Claustre *et al.*, 1992). The serotonin 5-HT_{2C} receptor is thought to be involved in numerous central processes, including mood, behaviour and appetite (Burris *et al.*, 1991; Kennett & Curzon, 1988; Kennett *et al.*, 1989; Sanders-Bush & Breeding, 1991). For this reason, ligands that interact with this receptor are of clinical interest. Antagonists, for example, might be useful for the treatment of anxiety (Kennett *et al.*, 1989), schizophrenia (Canton *et al.*, 1990), obsessive–compulsive or panic disorders (Kahn & Wetzler, 1991). As 5-HT_{2C} agonists have been found to have mood-elevating properties in healthy volunteers, they might have antidepressant activity (Berendsen, 1995). The effects of antagonists and agonists are very different and thus it is important to understand which structural properties determine the 5-HT_{2C} activities of ligands.

After the discovery of the 5-HT_{2C} receptor, the phenylpiperazines (see Fig. 1), which were already known as central 5-HT ligands, were tested for their specific actions at this receptor. These actions, in relation to the structural characteristics of these compounds, are the topic of the present paper. We restrict ourselves to phenylpiperazines that are only substituted at the positions *ortho* or *meta* to the piperazine ring. Well known phenylpiperazine derivatives of this type include 1-[3-(trifluoromethyl)phenyl]piperazine (TFMPP), 1-(3-chlorophenyl)piperazine (mCPP), 1-(1-naphthyl)piperazine (1NP) and eltoprazine. In 1987 Conn & Sanders-Bush (1987) first determined the activities of TFMPP, mCPP and 1NP at the 5-HT_{2C} receptor: in rat choroid plexus, TFMPP and mCPP both acted as partial to full agonists in the activation of phosphoinositide turnover, whereas 1NP acted as a full antagonist. These data were confirmed by the results of other authors (Claustre *et al.*, 1992; Schoeffter & Hoyer, 1989). *In vivo* experiments

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also indicate that 1NP opposes the activities of agonists at the 5-HT_{2C} receptor: it was found that 1NP opposes both mCPP-induced hypoactivity and hypophagia in rats (Kennett & Curzon, 1988; Kennett *et al.*, 1989). The relatively new 5-HT ligand eltoprazine was also shown to be an antagonist at the 5-HT_{2C} receptor, as it inhibits 5-HT-induced accumulation of inositol phosphates in pig choroid plexus (Sijbesma *et al.*, 1990).

For two derivatives of mCPP (Fillers & Hawkinson, 1979; Madding *et al.*, 1985) crystal structures were reported [CSD (Cambridge Structural Database) reference codes: CPTAZP and FOPYUE; Allen *et al.*, 1991). Recently, we determined the crystal structure of eltoprazine hydrochloride (Verdonk *et al.*, 1992). In addition, we intended to determine the structures of 1NP, TFMPP and two new 5-HT_{2C} ligands: 1-(2-methoxyphenyl)piperazine (oMPP) and 1-(3-methoxyphenyl)piperazine (mMPP). 1NP and TFMPP exhibit unfavourable crystallization characteristics, whereas the 4-methylated analogues are much easier to crystallize. The presence of a 4-methyl group is not likely to affect the conformation of the molecule. Therefore, we will consider the crystal structures of the 4-methylated analogues of 1NP, 1-(1-naphthyl)-4-methylpiperazine (1NMP), and that of TFMPP, 1-[(3-trifluoromethyl)phenyl]-4-methylpiperazine (TFMPMP), as representatives for the non-methylated compounds.

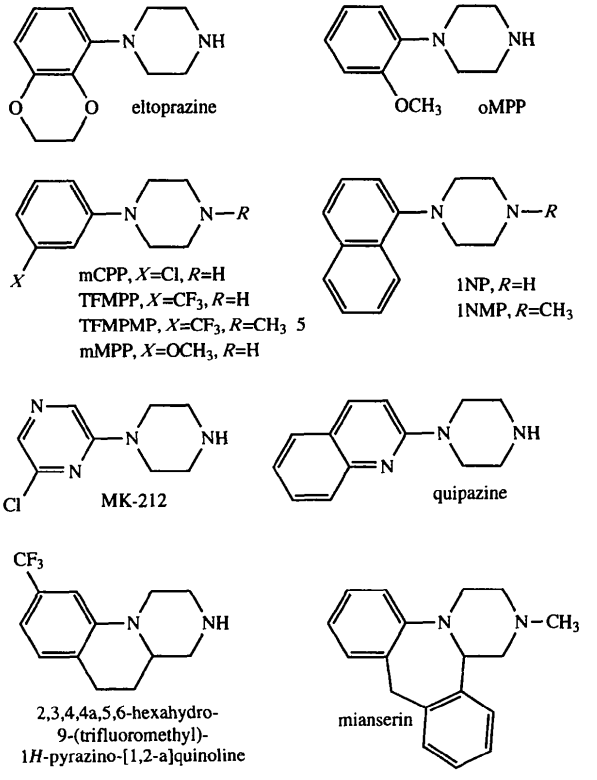

Fig. 1. Two-dimensional representations of the phenylpiperazines that are discussed in this paper.

2. Materials

The hydrochloride salts of 1NP, mCPP, TFMPP and oMPP, and the malcate salt of mMPP were kindly supplied by NV Organon (Oss, The Netherlands). 1NMP and TFMPMP were synthesized according to a procedure given in the literature (Ten Hoeve *et al.*, 1993), except for the work-up procedure. In our case, water was added to the reaction mixture at room temperature. The resulting mixture was extracted with pentane three times. The combined organic fractions were dried over potassium carbonate and concentrated *in vacuo*. Distillation at water vapour pressure (TFMPMP) and oil pressure (1NMP) yielded the compounds as colourless oils (1NMP solidifies upon standing).

3. Crystal structure determinations

Crystallographic and refinement data for all structures are represented in Table 1. The crystals were mounted on an Enraf–Nonius CAD-4 diffractometer using Zr-filtered Mo $K\alpha$ radiation. The lattice parameters were determined by least-squares refinement of 25 reflections using the SET4 method (De Boer & Duisenberg, 1984). Lorentz–polarization corrections were applied. The space groups were determined from the observed systematic absences, *HELENA* (Spek, 1990*a*) was used for data reduction and the structures were determined by means of the automatic direct-methods routine in *SHELXS*86 (Sheldrick, 1985). The structures were refined with the *SHELXL*92 program (Sheldrick, 1992). *PLUTON* and *PLATON* (Spek, 1990*b*) were used to prepare the material for publication.

3.1. *NMP maleate*

1NMP maleate crystals were obtained by cooling a saturated (338 K) ethanolic solution to room temperature with subsequent slow evaporation of the solvent. After 1 d large, colourless, block-shaped crystals precipitated. The crystal that was used for the X-ray diffraction experiment was cut from a large crystal.

Positional and anisotropic displacement parameters for all non-H atoms and one overall isotropic displacement parameter for the H atoms were refined. Positional parameters were refined for all H atoms, except those of the methyl group (which were included at their calculated positions, riding on their parent atoms).

3.2. *TFMPMP maleate*

Crystals of TFMPMP maleate were obtained from a hot (338 K) saturated 1:10 mixture of hexane:ethanol, which was cooled down to room temperature. After 1 d large, colourless, square plate crystals precipitated. The data of the TFMPMP maleate crystal were collected at 190 K, in order to reduce the considerable thermal motion of the trifluoromethyl group that was observed at room temperature.

Table 1. *Experimental details*

	1NMP	mMPP	oMPP	TFMPMP
Crystal data				
Chemical formula	$C_{15}H_{19}N_2^+.C_4H_3O_4^-$	$C_{11}H_{17}N_2O^+.C_4H_3O_4^-$	$C_{11}H_{17}N_2O^+.C_6H_2N_3O_7^-$	$C_{12}H_{16}F_3N_2^+.C_4H_3O_4^-$
Chemical formula weight	342.40	308.34	421.37	360.34
Cell setting	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/a$	$P2_1/c$	$P\bar{1}$	$P2_1/c$
a (Å)	10.8834 (12)	6.5086 (11)	9.4085 (6)	15.910 (2)
b (Å)	11.2355 (10)	9.0954 (7)	9.8700 (6)	6.0477 (11)
c (Å)	14.743 (2)	26.686 (5)	10.9433 (7)	18.660 (2)
α (°)			77.563 (5)	
β (°)	104.295 (8)	93.325 (14)	81.341 (5)	108.028 (10)
γ (°)			81.080 (5)	
V (Å^3)	1747.0 (3)	1577.1 (4)	973.11 (11)	1707.3 (4)
Z	4	4	2	4
D_x (Mg m^{-3})	1.302	1.299	1.438	1.402
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
No. of reflections for cell parameters	25	25	25	25
θ range (°)	5.70–16.04	3.96–12.61	9.20–17.76	12.50–19.44
μ (mm^{-1})	0.09	0.10	0.12	0.12
Temperature (K)	293 (2)	293 (2)	293 (2)	293 (2)
Crystal form	Block shaped	Platelet	Block shaped	Square plate
Crystal size (mm)	0.48 × 0.31 × 0.10	0.19 × 0.08 × 0.03	0.30 × 0.25 × 0.20	0.81 × 0.80 × 0.13
Crystal colour	Colourless	Colourless	Yellow	Colourless
Data collection				
Diffractometer	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4
Data collection method	$\omega/2\theta$ scans with $\Delta\omega = 0.80 + 0.35\tan\theta$	$\omega/2\theta$ scans with $\Delta\omega = 0.91 + 0.35\tan\theta$	$\omega/2\theta$ scans with $\Delta\omega = 0.61 + 0.35\tan\theta$	$\omega/2\theta$ scans with $\Delta\omega = 0.92 + 0.35\tan\theta$
Absorption correction	None	None	None	None
No. of measured reflections	6135	2770	9425	5002
No. of independent reflections	4011	2521	4443	3905
No. of observed reflections	1469	860	2890	2654
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.1943	0.0651	0.0246	0.0652
θ_{max} (°)	27.51	24.14	27.47	27.49
Range of h, k, l	$-14 \rightarrow h \rightarrow 14$ $-14 \rightarrow k \rightarrow 0$ $-19 \rightarrow l \rightarrow 19$	$0 \rightarrow h \rightarrow 7$ $0 \rightarrow k \rightarrow 10$ $-30 \rightarrow l \rightarrow 30$	$-12 \rightarrow h \rightarrow 12$ $-12 \rightarrow k \rightarrow 12$ $-14 \rightarrow l \rightarrow 14$	$-20 \rightarrow h \rightarrow 20$ $-7 \rightarrow k \rightarrow 0$ $-24 \rightarrow l \rightarrow 24$
No. of standard reflections	3	3	3	3
Intensity decay (%)	2	3	3	7
Refinement				
Refinement on	F^2	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0568	0.0759	0.0620	0.0534
$wR(F^2)$	0.1301	0.1947	0.1903	0.1468
S	0.830	0.858	1.089	1.047
No. of reflections used in refinement	4011	2521	4443	3905
No. of parameters used	284	204	272	230
H-atom treatment	See text	See text	See text	See text
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0470P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0759P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2 + (0.1021P)^2 + 0.0709P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0704P)^2 + 0.4534P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001	< 0.001	< 0.001	< 0.001
$\Delta\rho_{max}$ (e Å^{-3})	0.165	0.218	0.515	0.306
$\Delta\rho_{min}$ (e Å^{-3})	−0.181	−0.209	−0.309	−0.411
Extinction method	None	None	None	None
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C)	*International Tables for Crystallography* (1992, Vol. C)	*International Tables for Crystallography* (1992, Vol. C)	*International Tables for Crystallography* (1992, Vol. C)

Table 1 (*cont.*)

	lNMP	mMPP	oMPP	TFMPMP
Computer programs				
Cell refinement	*SET*4 (De Boer & Duisenberg, 1984)	*SET*4 (De Boer & Duisenberg, 1984)	*SET*4 (De Boer & Duisenberg, 1984)	*SET*4 (De Boer & Duisenberg, 1984)
Data reduction	*HELENA* (Spek, 1990*a*)	*HELENA* (Spek, 1990*a*)	*HELENA* (Spek, 1990*a*)	*HELENA* (Spek, 1990*a*)
Structure solution	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)	*SHELXS*86 (Sheldrick, 1985)
Structure refinement	*SHELXL*92 (Sheldrick, 1992)	*SHELXL*93 (Sheldrick, 1992)	*SHELXL*92 (Sheldrick, 1992)	*SHELXL*92 (Sheldrick, 1992
Preparation of material for publication	*PLATON* (Spek, 1990*b*)	*PLATON* (Spek, 1990*b*)	*PLATON* (Spek, 1990*b*)	*PLATON* (Spek, 1990*b*)

Positional and anisotropic displacement parameters for all non-H atoms and one overall isotropic displacement parameter for the H atoms were refined. Only the maleate H atom between the two O atoms could be located and refined; all other H atoms were included at their calculated positions, riding on their parent atoms.

3.3. *oMPP picrate*

oMPP picrate crystals were obtained by mixing equimolecular ethanolic solutions of oMPP hydrochloride and picric acid. After several days (at room temperature), good quality, yellow, block-shaped crystals appeared.

Positional and anisotropic displacement parameters for all non-H atoms and one overall isotropic displacement parameter for the H atoms were refined. All H atoms were included at their calculated positions, riding on their parent atoms.

3.4. *mMPP maleate*

mMPP maleate was dissolved in hot ethanol and, after cooling, small crystalline platelets were obtained.

Positional and anisotropic displacement parameters for all non-H atoms and one overall isotropic displacement parameter for the H atoms were refined. Only the maleate H atom between the two O atoms could be located and refined; all other H atoms were included at their calculated positions, riding on their parent atoms.

Views of the complete molecular structures and the atom labelling schemes are shown in Figs. 2(*a*)–(*d*).

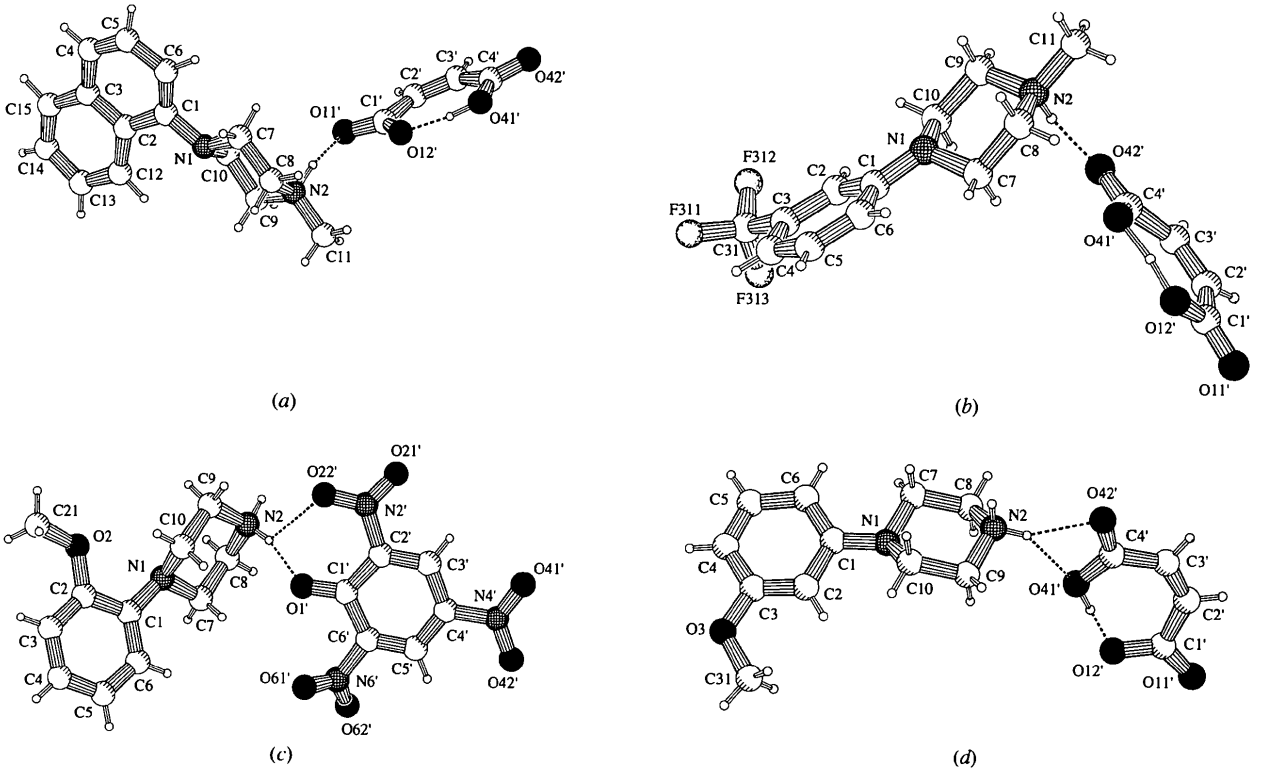

Fig. 2. Molecular structure and atomic labelling schemes of (*a*) lNMP maleate, (*b*) TFMPMP maleate, (*c*) oMPP picrate and (*d*) mMPP maleate.

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

	x	y	z	U_{eq}
(*a*) 1NMP				
N1	0.1421 (2)	0.0174 (2)	0.3297 (2)	0.0390 (6)
N2	−0.0025 (2)	0.1292 (2)	0.1621 (2)	0.0467 (6)
C1	0.2245 (2)	−0.0085 (2)	0.4190 (2)	0.0388 (7)
C10	0.2038 (3)	0.0753 (3)	0.2635 (2)	0.0442 (8)
C2	0.3208 (2)	−0.0961 (2)	0.4230 (2)	0.0409 (7)
C6	0.2114 (3)	0.0443 (3)	0.4998 (2)	0.0488 (8)
C8	−0.0629 (3)	0.0806 (3)	0.2352 (2)	0.0501 (8)
C3	0.4085 (3)	−0.1173 (3)	0.5101 (2)	0.0482 (8)
C7	0.0273 (3)	0.0839 (3)	0.3305 (2)	0.0491 (8)
C12	0.3312 (3)	−0.1647 (3)	0.3455 (3)	0.0531 (9)
C9	0.1202 (3)	0.0667 (3)	0.1658 (2)	0.0489 (8)
C13	0.4302 (3)	−0.2419 (3)	0.3523 (3)	0.0649 (10)
C4	0.3917 (3)	−0.0595 (3)	0.5917 (2)	0.0556 (9)
C11	−0.0913 (3)	0.1215 (3)	0.0677 (2)	0.0680 (10)
C15	0.5116 (3)	−0.1950 (3)	0.5122 (3)	0.0613 (10)
C14	0.5225 (3)	−0.2542 (3)	0.4358 (3)	0.0724 (12)
C5	0.2943 (3)	0.0152 (3)	0.5866 (2)	0.0573 (9)
O12′	0.0835 (2)	0.5694 (2)	0.8599 (2)	0.0701 (7)
O41′	0.1732 (2)	0.3701 (2)	0.8915 (2)	0.0718 (7)
O11′	−0.1049 (2)	0.6525 (2)	0.8362 (2)	0.0737 (7)
C1′	−0.0339 (3)	0.5651(3)	0.8540 (2)	0.0515 (8)
C3′	−0.0474 (3)	0.3414 (3)	0.8837 (2)	0.0567 (9)
O42′	0.1034 (2)	0.1898 (2)	0.9055 (2)	0.0970 (9)
C4′	0.0825 (3)	0.2962 (4)	0.8938 (2)	0.0623 (9)
C2′	−0.0939 (3)	0.4490 (3)	0.8692 (2)	0.0602 (9)
(*b*) mMPP				
N1	0.2480 (7)	0.5631 (5)	0.3416 (2)	0.0448 (13)
N2	0.1710 (7)	0.4804 (5)	0.4422 (2)	0.0521 (14)
O12′	−0.2444 (7)	0.3884 (5)	0.0346 (2)	0.0601 (13)
O41′	−0.2388 (7)	0.6521 (5)	0.0258 (2)	0.0625 (14)
O11′	−0.2409 (7)	0.1950 (5)	−0.0151 (2)	0.0681 (15)
O42′	−0.2191 (7)	0.8143 (5)	−0.0341 (2)	0.0693 (15)
C2	0.1395 (10)	0.6038 (6)	0.2546 (2)	0.049 (2)
O3	0.0455 (9)	0.6398 (6)	0.1666 (2)	0.088 (2)
C10	0.0396 (9)	0.5673 (8)	0.3602 (2)	0.064 (2)
C1	0.2773 (9)	0.6367 (6)	0.2966 (2)	0.043 (2)
C9	0.0195 (9)	0.4521 (7)	0.4011 (2)	0.050 (2)
C2′	−0.2657 (10)	0.4225 (7)	−0.0539 (2)	0.054 (2)
C3	0.1677 (12)	0.6666 (8)	0.2095 (3)	0.063 (2)
C1′	−0.2490 (9)	0.3278 (8)	−0.0085 (3)	0.049 (2)
C7	0.3996 (10)	0.5921 (7)	0.3827 (2)	0.061 (2)
C3′	−0.2604 (10)	0.5689 (7)	−0.0589 (2)	0.052 (2)
C6	0.4365 (11)	0.7315 (8)	0.2901 (3)	0.068 (2)
C8	0.3806 (10)	0.4796 (8)	0.4234 (2)	0.070 (2)
C4	0.3281 (15)	0.7586 (10)	0.2028 (3)	0.090 (3)
C5	0.4562 (13)	0.7919 (8)	0.2412 (3)	0.085 (3)
C4′	−0.2370 (10)	0.6860 (8)	−0.0205 (3)	0.058 (2)
C31	−0.1221 (14)	0.5403 (10)	0.1698 (3)	0.108 (3)
(*c*) oMPP				
N1	0.2856 (2)	0.3898 (2)	1.0437 (2)	0.0445 (4)
N2	0.4462 (2)	0.3887 (2)	0.8007 (2)	0.0485 (5)
O2	0.1772 (2)	0.6062 (2)	1.1567 (2)	0.0709 (6)
C1	0.1779 (2)	0.3701 (3)	1.1500 (2)	0.0464 (5)
C2	0.1231 (3)	0.4844 (3)	1.2093 (2)	0.0544 (6)
C3	0.0215 (3)	0.4675 (4)	1.3148 (3)	0.0683 (8)
C4	−0.0242 (3)	0.3388 (4)	1.3648 (3)	0.0762 (9)
C5	0.0278 (3)	0.2280 (4)	1.3089 (3)	0.0724 (8)
C6	0.1276 (3)	0.2428 (3)	1.2009 (2)	0.0585 (6)
C7	0.3717 (3)	0.2622 (2)	1.0128 (2)	0.0488 (5)
C8	0.4978 (3)	0.2982 (3)	0.9165 (2)	0.0519 (6)
C9	0.3508 (3)	0.5160 (3)	0.8297 (2)	0.0558 (6)
C10	0.2284 (3)	0.4760 (3)	0.9301 (2)	0.0529 (6)
C21	0.1077 (4)	0.7317 (3)	1.1932 (4)	0.0877 (11)
C1′	0.2908 (2)	0.1567 (2)	0.6477 (2)	0.0393 (5)

Table 2 (*cont.*)

	x	y	z	U_{eq}
O1′	0.2768 (2)	0.2239 (2)	0.73379 (15)	0.0542 (4)
C2′	0.3278 (2)	0.2089 (2)	0.5151 (2)	0.0386 (5)
N2′	0.3518 (2)	0.3544 (2)	0.4706 (2)	0.0474 (5)
O21′	0.4060 (2)	0.3889 (2)	0.3625 (2)	0.0713 (6)
O22′	0.3206 (3)	0.4362 (2)	0.5410 (2)	0.0920 (8)
C3′	0.3471 (2)	0.1276 (2)	0.4252 (2)	0.0413 (5)
C4′	0.3308 (2)	−0.0124 (2)	0.4604 (2)	0.0425 (5)
N4′	0.3551 (2)	−0.0979 (2)	0.3655 (2)	0.0540 (5)
O41′	0.3830 (3)	−0.0418 (2)	0.2548 (2)	0.0757 (6)
O42′	0.3497 (2)	−0.2243 (2)	0.4000 (2)	0.0723 (6)
C5′	0.2981 (2)	−0.0738 (2)	0.5864 (2)	0.0448 (5)
C6′	0.2766 (2)	0.0082 (2)	0.6737 (2)	0.0434 (5)
N6′	0.2436 (3)	−0.0585 (2)	0.8057 (2)	0.0615 (6)
O61′	0.1401 (4)	−0.0075 (3)	0.8661 (3)	0.1427 (14)
O62′	0.3131 (3)	−0.1667 (3)	0.8441 (2)	0.1038 (9)
(*d*) TFMPMP				
N1	0.18252 (11)	0.8699 (3)	0.17057 (9)	0.0190 (4)
N2	0.35218 (11)	0.6542 (3)	0.20533 (9)	0.0158 (3)
C1	0.09741 (14)	0.9491 (3)	0.16110 (12)	0.0203 (4)
C2	0.02225 (14)	0.8440 (4)	0.11438 (12)	0.0236 (5)
C3	−0.06106 (15)	0.9371 (4)	0.10216 (13)	0.0275 (5)
C31	−0.1403 (2)	0.8166 (5)	0.0539 (2)	0.0405 (7)
F311	−0.20650 (10)	0.9471 (3)	0.01827 (11)	0.0592 (5)
F312	−0.12313 (12)	0.6937 (4)	0.00107 (14)	0.0976 (10)
F313	−0.17320 (13)	0.6754 (4)	0.09348 (14)	0.0795 (7)
C4	−0.0725 (2)	1.1318 (4)	0.13666 (14)	0.0308 (5)
C5	0.0015 (2)	1.2354 (4)	0.18432 (14)	0.0292 (5)
C6	0.08493 (15)	1.1466 (3)	0.19646 (13)	0.0235 (4)
C7	0.24604 (13)	0.8739 (4)	0.24679 (11)	0.0197 (4)
C8	0.33932 (13)	0.8642 (3)	0.24288 (11)	0.0166 (4)
C11	0.44444 (13)	0.6383 (3)	0.20158 (11)	0.0185 (4)
C9	0.28587 (13)	0.6398 (3)	0.12857 (11)	0.0180 (4)
C10	0.19205 (13)	0.6661 (3)	0.13150 (12)	0.0202 (4)
O42′	0.40909 (10)	0.3439 (2)	0.61938 (8)	0.0249 (3)
O41′	0.40475 (10)	0.5881 (2)	0.53001 (8)	0.0211 (3)
O12′	0.37870 (11)	0.5810 (2)	0.39496 (8)	0.0240 (4)
O11′	0.34864 (11)	0.3282 (2)	0.30401 (8)	0.0264 (4)
C4′	0.40629 (13)	0.3852 (3)	0.55434 (11)	0.0180 (4)
C3′	0.40369 (14)	0.1970 (3)	0.50194 (12)	0.0187 (4)
C2′	0.38893 (14)	0.1943 (3)	0.42765 (12)	0.0200 (4)
C1′	0.37036 (14)	0.3815 (3)	0.37190 (11)	0.0190 (4)

Atomic coordinates and equivalent isotropic displacement parameters are listed in Table 2.† In all structures the piperazine rings are in the approximate chair conformation. The aromatic systems show little deviation from planarity, except in the case of 1NMP (see below). The balance of two oppositely directed forces determines the relative orientation of the phenyl and piperazine ring, which we will describe with the C(2)—C(1)—N(1)—Lp dihedral angle φ; Lp is the lone pair of the N(1) atom. This lone pair tends to form a hyperconjugated system with the aromatic ring, which can be optimally established if the lone pair is perpendicular to the plane of the aromatic ring ($\varphi = \pm 90°$). The steric repulsion, however, is maximal for this geometry and drives φ

† Lists of atomic coordinates, anisotropic displacement parameters and structure factors have been deposited with the IUCr (Reference: HA0157). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Selected bond lengths (Å), bond angles and dihedral angles (°)*

	1NMP	TFMPMP	oMPP	mMPP
C(1)—N(1)	1.428 (3)	1.395 (3)	1.424 (3)	1.397 (6)
C(1′)—O(11′)	1.237 (3)	1.248 (2)	–	1.222 (6)
C(1′)—O(12′)	1.260 (3)	1.274 (2)	–	1.276 (7)
C(4′)—O(41′)	1.297 (4)	1.306 (2)	–	1.275 (8)
C(4′)—O(42′)	1.221 (4)	1.226 (2)	–	1.229 (7)
C(1)—N(1)—C(7)	116.1 (2)	117.9 (2)	115.7 (2)	116.1 (5)
C(1)—N(1)—C(10)	114.7 (2)	118.2 (2)	113.2 (2)	116.9 (5)
C(7)—N(1)—C(10)	108.2 (2)	110.5 (2)	109.7 (2)	109.7 (5)
C(2)—C(1)—N(1)—Lp	49.2 (2)	109.7 (2)	44.2 (2)	62.2 (6)
C(4)—C(3)—C(2)—*X*(2)†	−172.8 (3)	–	−177.8 (3)	–
C(1)—C(2)—C(3)—*X*(3)‡	−173.6 (3)	−178.0 (2)	–	178.8 (8)
C(1)—C(2)—C(3)—C(4)	5.6 (4)	−1.4 (3)	1.7 (4)	2 (1)
C(2)—C(3)—C(4)—C(5)	−0.4 (5)	0.2 (4)	−1.6 (5)	−2 (1)
C(3)—C(4)—C(5)—C(6)	−4.2 (5)	0.5 (3)	0.1 (6)	2 (1)
C(4)—C(5)—C(6)—C(1)	3.7 (5)	0.1 (5)	1.3 (4)	0 (1)
C(5)—C(6)—C(1)—C(2)	1.7 (4)	−1.2 (3)	−1.2 (4)	−0.3 (9)
C(6)—C(1)—C(2)—C(3)	−6.2 (4)	1.9 (3)	−0.3 (4)	0.2 (9)

† *X*(2) represents C(12) for 1NMP and O(2) for oMPP. ‡ *X*(3) represents C(15) for 1NMP, C(31) for TFMPMP and O(3) for mMPP.

Table 4. *Geometries of hydrogen bonds and short C—H···O-type interactions*

D—H···A	*D*···*A* (Å)	*D*—H (Å)	H···*A* (Å)	*D*—H···A (°)	Symmetry code
1NMP maleate					
N(2)—H(21)···O(11′)	2.714 (3)	1.01 (3)	1.75 (3)	158 (2)	$-x, 1-y, 1-z$
O(41′)—H(41′)···O(12′)	2.441 (3)	0.95 (3)	1.49 (3)	171 (3)	
TFMPMP maleate					
N(2)—H(21)···O(11′)	2.710 (2)	0.910 (2)	1.816 (2)	166.8 (2)	
O(41′)—H(41′)···O(12′)	2.424 (2)	1.15 (2)	1.28 (2)	173 (2)	
C(7)—H(72)···O(11′)	3.205 (3)	0.970 (3)	2.558 (3)	124.2 (2)	$x, 1+y, z$
C(8)—H(81)···O(42′)	3.353 (2)	0.970 (3)	2.466 (2)	151.9 (2)	$x, 3/2-y, -1/2+z$
C(8)—H(82)···O(12′)	3.206 (2)	0.970 (3)	2.590 (2)	121.5 (2)	
C(9)—H(92)···O(41′)	3.438 (2)	0.970 (3)	2.580 (3)	147.6 (2)	$x, 3/2-y, -1/2+z$
C(11)—H(111)···O(42′)	3.262 (2)	0.960 (3)	2.358 (2)	156.7 (2)	$x, 1/2-y, -1/2+z$
C(11)—H(112)···O(42′)	3.433 (2)	0.960 (3)	2.473 (3)	179.0 (2)	$1-x, 1-y, 1-z$
oMPP picrate					
N(2)—H(21)···O(1′)	2.719 (3)	0.900 (3)	1.840 (3)	164.9 (2)	
N(2)—H(21)···O(22′)	3.156 (3)	0.900 (3)	2.592 (3)	121.4 (2)	
N(2)—H(22)···O(21′)	2.907 (3)	0.900 (3)	2.189 (3)	136.4 (2)	$1-x, 1-y, 1-z$
C(8)—H(82)···O(41′)	3.421 (3)	0.970 (4)	2.557 (3)	148.5 (2)	$1-x, -y, 1-z$
C(9)—H(92)···O(62′)	3.132 (4)	0.970 (4)	2.545 (4)	119.0 (3)	$x, y+1, z$
mMPP maleate					
N(2)—H(21)···O(41′)	3.130 (7)	0.901 (7)	2.414 (6)	136.5 (5)	$-x, y-1/2, 1/2-z$
N(2)—H(21)···O(42′)	2.882 (7)	0.901 (7)	2.034 (7)	156.5 (5)	$-x, y-1/2, 1/2-z$
N(2)—H(22)···O(11′)	2.775 (7)	0.900 (7)	2.019 (7)	140.7 (5)	$-x, y+1/2, 1/2-z$
O(41′)—H(41′)···O(12′)	2.411 (6)	1.08 (9)	1.34 (9)	166 (6)	
C(8)—H(82)···O(42′)	3.353 (8)	0.970 (8)	2.594 (8)	135.2 (6)	$x+1, 3/2-y, 1/2+z$
C(9)—H(91)···O(11′)	3.180 (8)	0.970 (8)	2.518 (8)	125.3 (6)	$x, 1/2-y, 1/2+z$
C(9)—H(92)···O(3)	3.384 (8)	0.970 (9)	2.476 (8)	155.0 (6)	$-x, y-1/2, 1/2-z$

towards $\varphi = 0$ and 180°, especially when the phenyl ring is substituted *ortho* to the piperazine ring. This becomes clear from the intramolecular geometries in Table 3. If φ is close to ±90°, the C(1)—N(1) bond length is shorter than in cases for which φ deviates more from ±90° (for the *ortho*-substituted compounds). The same effect, but to a lesser extent, can be seen in the bond angles of the N(1)[C(1)C(7)C(10)] group: this group is slightly more planar if there are no *ortho* substituents, which favours hyperconjugation. The hyperconjugation force appears to be rather strong as the attempt to drive φ towards $\varphi = \pm 90°$ results in a considerable distortion of the planarity of the aromatic system in 1NMP.

The hyperconjugation of the lone pair of N(1) with the aromatic system is probably also the reason why N(2) is protonated, rather than N(1), and why N(1) is not involved in hydrogen bonding in any of these structures. The geometries of the intra- and intermolecular hydrogen bonds and CH···O type interactions are listed in Table 4. The position of the maleate H atom which is located

between O(12′) and O(41′) in the structures of 1NMP, TFMPMP and mMPP maleate is not very accurate. In TFMPMP maleate this proton refined to a position approximately halfway between O(12′) and O(41′), although the geometries of the maleate carboxylate groups are rather asymmetric. On the other hand, in the structure of mMPP maleate, the geometries of the maleate carboxylate groups are rather symmetric, although, in the refined structure, the proton between the O atoms appears to be attached to O(41′). C—H···O-type interactions are frequently observed in these structures. It is interesting to notice that these contacts are almost exclusively formed by C atoms that are attached to the charged N atoms.

4. Conformation and activity

We found that the affinity of a phenylpiperazine for the 5-HT$_{2C}$ receptor is correlated with the hydrophobicity of its *ortho* and/or *meta* substituent (Verdonk, 1995). In the present paper, however, we will focus on the conformational characteristics of these compounds in relation to their 5-HT$_{2C}$ activity. For this purpose, a conformational analysis on the six compounds of interest, *i.e.* mCPP, TFMPP, 1NP, eltoprazine, oMPP and mMPP, was carried out. In the 43 crystal structures of phenylpiperazines and related compounds that can be found in the CSD (Allen *et al.*, 1991), the phenyl substituent of the piperazine ring is always in the equatorial position. NMR studies have also shown that the *N* substituents on a piperazine ring occupy the equatorial position (Lett *et al.*, 1970). Therefore, we only considered these conformations and neglected those where the phenyl ring is in the axial position. For the same reason, the conformation of the piperazine ring was assumed to be an idealized chair. The major degree of freedom that remains is the rotation about the central phenyl—N bond, described by the parameter φ.

In 1994 we determined the torsion barrier for *N,N*-dimethylaniline and related compounds for the MM2(87) force field, by means of the ToBaD method (Verdonk *et al.*, 1994). This torsion barrier, in combination with the MM2(87) force field, was used to calculate the free energy as a function of φ for the six *ortho*- and *meta*-substituted phenylpiperazines. The method of prudent ascent was used to scan the φ space (Hooft *et al.*, 1991). The results of these calculations are represented in Fig. 3, where they are compared with the crystal structures of the corresponding compounds. It appears that the calculations are in very good agreement with the crystal structures: the crystal structure conformation is always within 1.26 kJ mol^{-1} of the minimum-energy conformation. Therefore, we feel that the conformational freedom concerning φ in this type of compound can be described rather accurately with this force field. Dijkstra (1993) concluded that the conformational behaviour of phenylpiperazines is mainly determined by the electron-donating or -withdrawing effects of the substituents on the phenyl ring. For the compounds we investigated these effects seem to be less important, as we are able to describe the conformational behaviour of the phenylpiperazines by means of a molecular mechanics approach (which does not include the electron-donating or -withdrawing effects of ring substituents).

There is a relation between the conformational freedom concerning φ and the 5-HT$_{2C}$ receptor activity. The agonists TFMPMP and mCPP have a global minimum-energy conformation around $\varphi = \pm 100°$. However, in fact all conformations with $60 \leq |\varphi| \leq 125°$ are within 2.09 kJ mol^{-1} of the global minimum and therefore very easy to access. For the antagonists 1NP and eltoprazine, however, the conformations with $75 \leq |\varphi| \leq 105°$ are difficult to access, caused by a substituent *ortho* to the piperazine ring. For this reason, it is likely that a conformation within one of these φ intervals is needed for 5-HT$_{2C}$ receptor activation.

This idea is supported by the actions at the 5-HT$_{2C}$ receptor of two related compounds: MK212 and quipazine. We found that these compounds have their calculated global minimum-energy conformation at $\varphi = \pm 90°$. In agreement, MK212 and quipazine were both

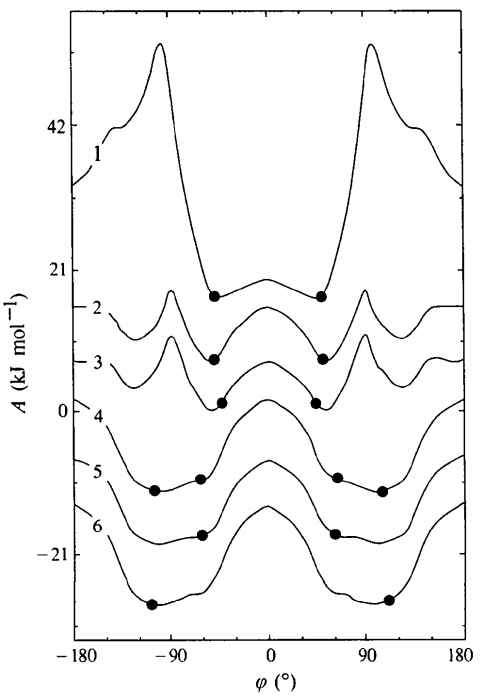

Fig. 3. The solid lines represent the free energy of 1NMP (1), eltoprazine (2), oMPP (3), mCPP (4), mMPP (5) and TFMPMP (6) as a function of the phenyl–N dihedral angle φ, calculated with the ToBaD torsion barrier. The filled circles represent the actual values of φ in crystal structures of these compounds or representative derivatives, *i.e.* 1NMP (1), eltoprazine (2), oMPP (3), two N(2) substituted mcpp derivatives (CSD refcodes CPTAZP and FOPYUE) (4), mMPP (5) and TFMPMP (6).

reported to be agonists at the 5-HT_{2C} receptor (Claustre *et al.*, 1992; Conn & Sanders-Bush, 1987; Schoeffter & Hoyer, 1989). Furthermore, the antidepressant mianserin is a conformationally restricted analogue, in which a bridge between the phenyl ring and the piperazine ring fixes φ at approximately 39° (CSD refcodes: BUCVAW, HIJDEJ and MIANSB); this compound is a strong inverse 5-HT_{2C} agonist (Barker *et al.*, 1994). Moreover, in 1985 Huff and colleagues found that a structurally rigid phenylpiperazine, 2,3,4,4a,5,6-hexahydro-9-(trifluoromethyl)-1*H*-pyrazino-[1,2*a*]-quinoline, for which the phenyl ring and the piperazine ring are approximately co-planar, showed serotoninmimetic (agonistic) effects *in vivo* (Huff *et al.*, 1985).

The actions at the 5-HT_{2C} receptor of oMPP and mMPP may be predicted from these findings. As they are both approximately as hydrophobic as eltoprazine, they are expected to have approximately the same affinity at the 5-HT_{2C} receptor. In agreement with the preliminary results indicate that both oMPP and mMPP have 5-HT_{2C} affinities that are comparable to that of eltoprazine (Organon, 1995). mMPP can easily adopt the presumed activating conformation and is therefore predicted to be an agonist. Again, preliminary studies show that this compound is able to increase phosphoinositide turnover in rat choroid plexus, with an efficacy that is comparable to that of TFMPP and mCPP (Organon, 1995). oMPP is predicted to be an antagonist, because the *ortho*-methoxy substituent limits the accessibility of the presumed activating conformation. Recent experiments indicate that, indeed, oMPP is able to block 5-HT_{2C}-induced behaviour in rats (Organon, 1995).

As our prediction that the ±90° conformation is responsible for the activation of the 5-HT_{2C} receptor was confirmed by *in vitro* and *in vivo* tests, we are confident that this hypothesis is correct. In the future it can be of help to design new, more potent, 5-HT_{2C} ligands that may lead to novel psychiatric drugs.

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