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PHENOTHIAZINE DRUGS AND METABOLITES: MOLECULAR CONFORMATION AND DOPAMINERGIC, ALPHA ADRENERGIC AND MUSCARINIC CHOLINERGIC RECEPTOR BINDING

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Abstract—The solid state molecular structures of methoxypromazine and *N*-monodesmethyl chlorpromazine sulphoxide were determined by X-ray crystallography, as an extension of previous studies on the molecular structures of chlorpromazine sulphoxide and methotrimeprazine sulphoxide. The binding affinities of phenothiazine drugs and metabolites with known crystal structures to dopaminergic, alpha adrenergic and muscarinic cholinergic receptors in rat brain were examined using radio-ligand binding techniques. Comparison of their solid state molecular structures and potencies in neurotransmitter receptor binding reveals that these compounds exist in two different conformations: One, associated with low biological activity, has an angle between the planes of the two aryl rings in the range of 155–160°, and a torsion angle of −80 to −84° around the N(10)–C bond of the side-chain, calculated from the substituted benzene ring. In the other conformation, which is found in the biologically active derivatives, the angle between the planes of the two aryl rings is in the range of 134–145°, and the torsion angle around the N(10)–C bond of the side-chain is in the range of 64–69° or 129–144°. The "active" and "inactive" conformations thus have the side-chain on opposite sides of the ring system.

A substantial body of evidence has demonstrated that neuroleptic drugs exert their clinical effects mainly through antagonism of dopamine receptors in the brain [1, 2], as originally suggested by Carlsson and Lindqvist in 1963 [3]. Sub-groups of dopamine receptors have been identified, one (D1) associated with adenylate cyclase, and another (D2) not linked with the adenylate cyclase, which is labelled by ^{3}H-butyrophenones [2]. It has been suggested that both receptors may exist in two different, interconvertible states [4]. Although phenothiazine drugs are active in binding to both D1 and D2 receptors, the current concept is that their antipsychotic action is mediated mainly via the D2 receptors [2, 5].

Many structure–activity relationship studies have been done in the search for an active conformation of neuroleptics [6–14], but the molecular conformational requirements for the therapeutic effects of antipsychotic drugs are still obscure. It has been suggested that phenothiazines mimic the 3-dimensional *trans* conformation of dopamine in their interaction with dopamine receptors in the brain [15], and also that this conformational similarity is due to Van der Waals interactions between the 2-substituent on the phenothiazine nucleus and the nitrogen atom at the side-chain [16]. The latter hypothesis has, however, been rejected by others on the basis of interatomic distances in the known crystal structures of psychoactive phenothiazines [17]. Potential energy calculations and comparisons of the solid state structures of a number of phenothiazine derivatives indicate that the influence of the 2-substituent on the neuroleptic potency is due to direct interaction between this substituent and the receptor, and not to conformational changes induced by the 2-substituent in the rest of the molecule [11, 17, 18].

Potential energy calculations [18] have demonstrated a certain rotational degree of freedom of the side-chain of the phenothiazine derivatives, especially for bond No. 4 in Fig. 1. In general, the resemblance of solid state molecular conformations to the conformation at the dopamine receptor has been questioned for antipsychotic drugs having flexible molecular structures [1, 10].

Many antipsychotic drugs also have high binding affinities to central α-adrenergic receptors, and the relative affinities for α1 adrenergic and dopaminergic D2 receptor binding sites have been proposed as an index of their relative potencies in eliciting side-effects like orthostatic hypotension and sedation [19, 20]. The clinical potencies of a series of neuroleptic drugs showed, however, no correlation with their potencies in *in vitro* α1-adrenergic receptor binding [21]. Schizophrenic patients had an increased number of α2-receptor binding sites in platelets, and the authors suggested that alterations in central adrenergic transmission might play a role in schizophrenia [22].

The potency of neuroleptic drugs in *in vitro* binding to central muscarinic cholinergic receptors is related to their tendency to give peripheral parasympatolytic side-effects such as dry mouth and exacerbation of glaucoma, and is also inversely related to their tendency to give extrapyramidal side-effects [23, 24].

The solid state molecular conformations of methotrimeprazine (levomepromazine), methotrimeprazine sulphoxide and clorpromazine sulphoxide, and

their binding affinities to central dopaminergic D2 and α1-adrenergic receptors in the rat, were reported in a preceding paper [25]. The present report presents the solid state molecular structures of methoxypromazine and *N*-monodesmethyl chlorpromazine sulphoxide, and *in vitro* binding affinities of these and other phenothiazine drugs and drug metabolites with known crystal structures, to central dopaminergic D2, α1- and α2-adrenergic, and muscarinic cholinergic M1 receptors in the rat.

METHODS

Molecular structures. Methoxypromazine (MPR) and *N*-monodesmethyl chlorpromazine sulphoxide (DCPZSO), in the form of free bases, were generously donated by Rhône-Poulenc Industries, Paris, France. Single crystals were obtained by evaporation of an *m*-xylene solution of MPR at room temperature, and by slow cooling of a hexane solution of DCPZSO in a sealed glass capillary, in a thermo flask. The space groups were determined by Weissenberg film technique, and the densities were determined by the flotation method.

The reflection intensities were recorded at −150° with a computer-controlled CAD4 automatic diffractometer, using graphite-monochromated Cu-Kα radiation. The structures were solved using the MULTAN program package [26], by the multiple tangent-formula direct method. Full crystallographic data will be published elsewhere.

Receptor binding. The binding affinities of chlorpromazine, methoxypromazine, methotrimeprazine and some of their metabolites to dopaminergic D2, α1-adrenergic, α2-adrenergic and muscarinic cholinergic M1 receptors were studied in brains from male Sprague–Dawley rats, by essentially the same technique as in a previous study [27]. The following radioligands and specific displacers were used: ^{3}H-WB4101 and norepinephrine for α1-adrenergic, ^{3}H-yohimbine and norepinephrine for α2-adrenergic, ^{3}H-quinuclidinyl benzilate (^{3}H-QNB) and oxotremorine for muscarinic cholinergic M1, and ^{3}H-spiroperidol and +butaclamol for dopaminergic D2 receptor binding.

The experiments were repeated on 4–6 different days, using four different drug or metabolite concentrations in each experiment.

RESULTS

The crystals of DCPZSO were orthorhombic, space group Pbca, with eight molecules in the unit cell. Cell dimensions: a = 8.008, b = 19.051, c = 19.604 Å. The structure was refined to R = 0.04 using isotropic temperature factors for the hydrogen atoms and anisotropic temperature factors for the other atoms.

MPR crystallized in the monoclinic space group $P2_1/n$ with four molecules in the unit cell, and cell dimensions a = 7.462, b = 17.223, c = 12.745 Å, β = 96.18°. The structure was refined to $R = 0.07$ with isotropic thermal parameters for the H atoms and anisotropic temperature factors for the other atoms.

The O atom of the SO group in sulphoxide metabolites of phenothiazine drugs may theoretically attain two different positions, as illustrated in Fig. 2. The SO group in DCPZSO had a boat axial orientation, as in methotrimeprazine sulphoxide and chlorpromazine sulphoxide [25].

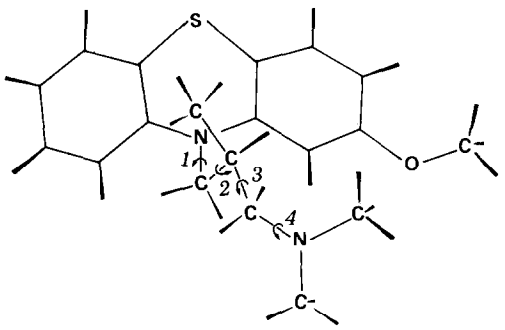

Fig. 1. Structure of methotrimeprazine [25], showing the four torsion angles of the side-chain. Torsion angles (A, B, C, D) are defined as positive for a clockwise rotation of A towards D and negative for counterclockwise rotation, when viewing along the line B to C.

The structure of DCPZSO resembles that of chlorpromazine sulphoxide (CPZSO), and has an angle of 155.3° between the planes of the two aryl rings (Table 1). Torsion angles Nos 1–3 of the side-chain (Fig. 1) are given in Table 1 for DCPZSO and some congeners, together with the distances of the terminal N atom of the side-chain from the centroids of the two aryl rings. ORTEP plots of the same compounds are shown in Fig. 3. As evident from Table 1 and Fig. 3, the six derivatives fall into two distinct conformational groups. One group, consisting of CPZSO, DCPZSO, and methoxypromazine maleate, have an angle of 155–160° between the planes of the aryl rings, and a conformation of

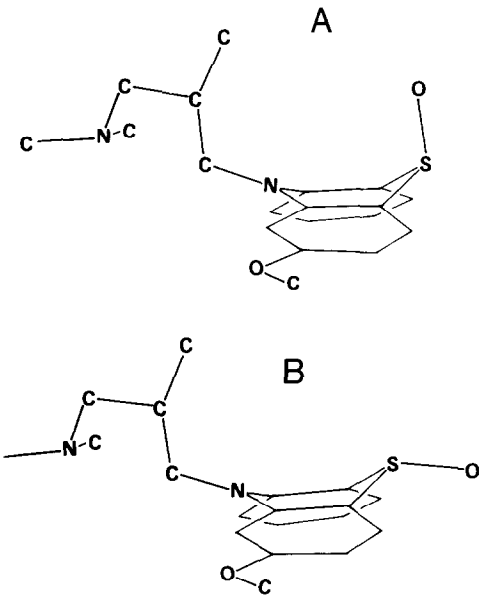

Fig. 2. Structure of methotrimeprazine sulphoxide showing two theoretically possible conformations of the SO group. A: axial, B: equatorial.

Table 1. Angle between planes of the benzene rings, torsion angles of the side-chain*, and distance of the terminal nitrogen atom from the centre of the substituted (N-A) and unsubstituted benzene rings (N-B), in the solid state structures of phenothiazine drugs and metabolites†

Compound‡ (Ref. No.)	Angle between benzene rings (°)	Torsion angle (°)			Distance (Å)	
		1	2	3	N-A	N-B
MET	138.0	69.3	−163.0	66.7	5.05	6.84
METSO	144.7	63.9	−162.5	67.0	5.01	6.84
CPZ [28]	139.4	68.7	−164.2	69.2	5.12	6.81
7-OHCPZ [29]	138.7	141.3	−176.3	58.7	6.11	6.43
CPZSO	159.5	−83.9	154.0	−72.6	4.85	6.63
DCPZSO	155.3	−81.8	160.3	74.0	6.67	5.69
MPR	134.3	64.3	−155.5	71.0	4.79	6.70
MPR maleate [30]	157.7	−80.3	175.5	−170.3	6.36	6.64

* The torsion angles are numbered according to Fig. 1. Torsion angle No. 1 is calculated from the adjacent C atom on the substituted benzene ring.

† Data acquired at room temperature for CPZ, 7-OHCPZ and MPR maleate, and at −150° for the other compounds.

‡ Abbreviations explained in Fig. 3.

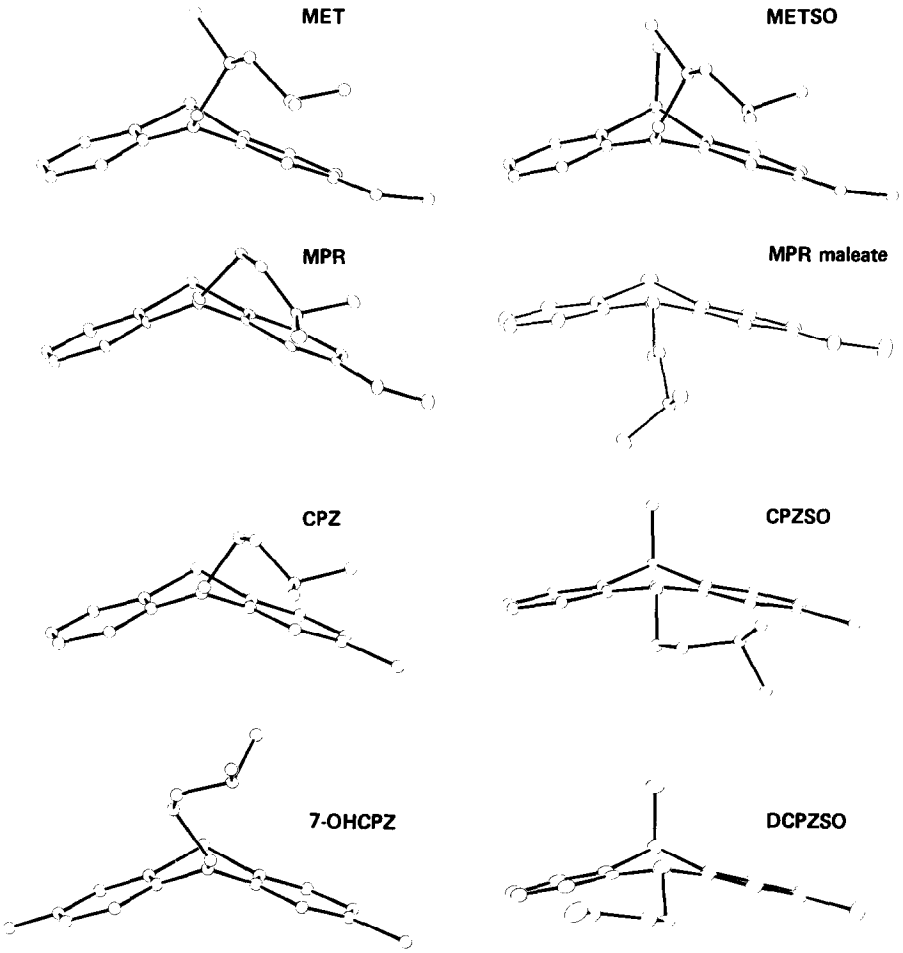

Fig. 3. ORTEP plots of methotrimeprazine (levomepromazine) (MET), methotrimeprazine sulphoxide (METSO), methoxypromazine (MPR), methoxypromazine maleate (MPR maleate), chlorpromazine (CPZ), chlorpromazine sulphoxide (CPZSO), *N*-monodesmethyl chlorpromazine sulphoxide (DCPZSO) and 7-hydroxy chlorpromazine (7-OHCPZ). Hydrogen atoms and the maleate ion have been omitted for clarity.

Table 2. Binding affinity to dopamine D2, α1-adrenergic, α2-adrenergic and muscarinic cholinergic M1 receptors in rat brain. IC_{50}: Concentration required to displace 50% of specific radioligand binding

Compound*	IC_{50} (nM)†			
	Dopamine D2 (striatum)	α1-Adrenergic (cortex)	α2-Adrenergic (cortex)	M1 Cholinergic (cortex)
MET	59 ± 2	3.1 ± 1.6	1200 ± 46	,330 ± 5
METSO	110,000 ± 1140	230 ± 33	74,000 ± 688	5100 ± 28
CPZ	50 ± 3	10 ± 3	1500 ± 36	430 ± 6
7-OHCPZ	80 ± 5	17 ± 4	4100 ± 64	2000 ± 37
CPZSO	49,000 ± 300	2100 ± 92	107,000 ± 1200	13,000 ± 53
DCPZSO	33,000 ± 250	880 ± 27	42,000 ± 305	25,000 ± 65
MPR	183 ± 12	7.2 ± 3.2	4100 ± 112	850 ± 10

* Abbreviations explained in Fig. 3.
† Mean values ± S.E.M. from 3–14 experiments.

the side-chain which is characterized by torsion angle No. 1 in the range of −80° to −84°. This places most of the side-chain and the terminal amino group "below" the ring system when viewed along the N–S axis of the thiazine ring, as shown in Fig. 3.

The other four compounds, methoxypromazine (MPR), methotrimeprazine (levomepromazine) (MET), methoxypromazine sulphoxide (METSO), chlorpromazine (CPZ) and 7-hydroxy chlorpromazine (7-OHCPZ), are more folded along the N–S axis, the angle between the planes of the two benzene rings being in the range of 134–145°. Torsion angle No. 1 of the side-chain (Fig. 1) is 141° in 7-OHCPZ and in the range of 64–69° in MPR, MET, METSO and CPZ, such that the side-chain lies "above" the ring system when viewed in the projection of Fig. 3.

Table 2 shows the binding affinities of the compounds included in Fig. 3 to dopaminergic D2, α1- and α2-adrenergic, and muscarinic cholinergic M1 receptors in rat brain. Chlorpromazine was the most potent compound in dopaminergic D2 and muscarinic cholinergic M1 receptor binding, and methotrimeprazine was the most potent in both types of alpha adrenergic receptor binding, which is in agreement with previously published data on these two compounds [31]. Among the metabolites, only 7-OHCPZ was active in dopaminergic D2 receptor binding, and it was also the most potent in α-adrenergic and muscarinic cholinergic receptor binding. The observed potencies of 7-OHCPZ in dopaminergic D2, α1 adrenergic and muscarinic cholinergic M1 receptor binding are in good agreement with previously published data on this metabolite [32, 33].

The sulphoxide metabolites generally had low potencies in all binding systems, compared to the parent compounds (Table 2). METSO was the least potent sulphoxide metabolite in dopaminergic D2 receptor binding, while it was six times more potent than DCPZSO and 14 times more potent than CPZSO in α1-adrenergic receptor binding. DCPZSO was more potent than CPZSO in dopaminergic D2, α1- and α2-adrenergic receptor binding.

As might have been expected, methotrimeprazine had similar binding characteristics in the form of its maleate salt and as the free base, dissolved in dilute acetic acid. The results for MPR in Table 2 are from experiments with both the free base and the maleate salt.

DISCUSSION

The data shown in Table 2 confirm the concept from pharmacodynamic studies of DCPZSO and CPZSO as pharmacologically inactive metabolites [34], and of METSO at less active than CPZ and MET, but more potent than CPZSO in some biological systems [35].

The energy barriers for rotation of the side-chain are smallest for bond No. 4 (Fig. 1) and largest for bond No. 1 [18, 36]. The similarity of the solid state molecular conformations of several psychoactive phenothiazine derivatives could point towards this as the energetically preferred conformation, which also has been found by theoretical calculations [36]. The most striking finding in the present study is the difference in conformations of the side-chain between the two groups of derivatives, CPZSO and DCPZSO versus MPR, MET, METSO, CPZ and 7-OHCPZ, which appear to be related to their pharmacological activities and potencies in neurotransmitter receptor binding.

The fact that the molecular conformation of methoxypromazine maleate is different from that of other psychoactive phenothiazines has been used to illustrate a postulated lack of relationship between the solid state molecular conformations and pharmacological activities of antipsychotic drugs having flexible molecular structures. It was of interest, therefore, to examine the solid state molecular structure of the free base of MPR. The finding that this structure has almost the same molecular conformation as that of CPZ and other psychoactive phenothiazine derivatives (Fig. 3) suggests that the "atypic" conformation first observed for MPR maleate is due to crystal forces induced by the maleate ion. The terminal N atom of the side-chain forms a strong hydrogen bond with one of the O atoms of a neighbouring maleate ion in methoxypromazine maleate [30]. A side-chain conformation similar to that in methoxypromazine maleate was also observed for the 1 : 1 complex of chlorpromazine and a copper chloride complex [37].

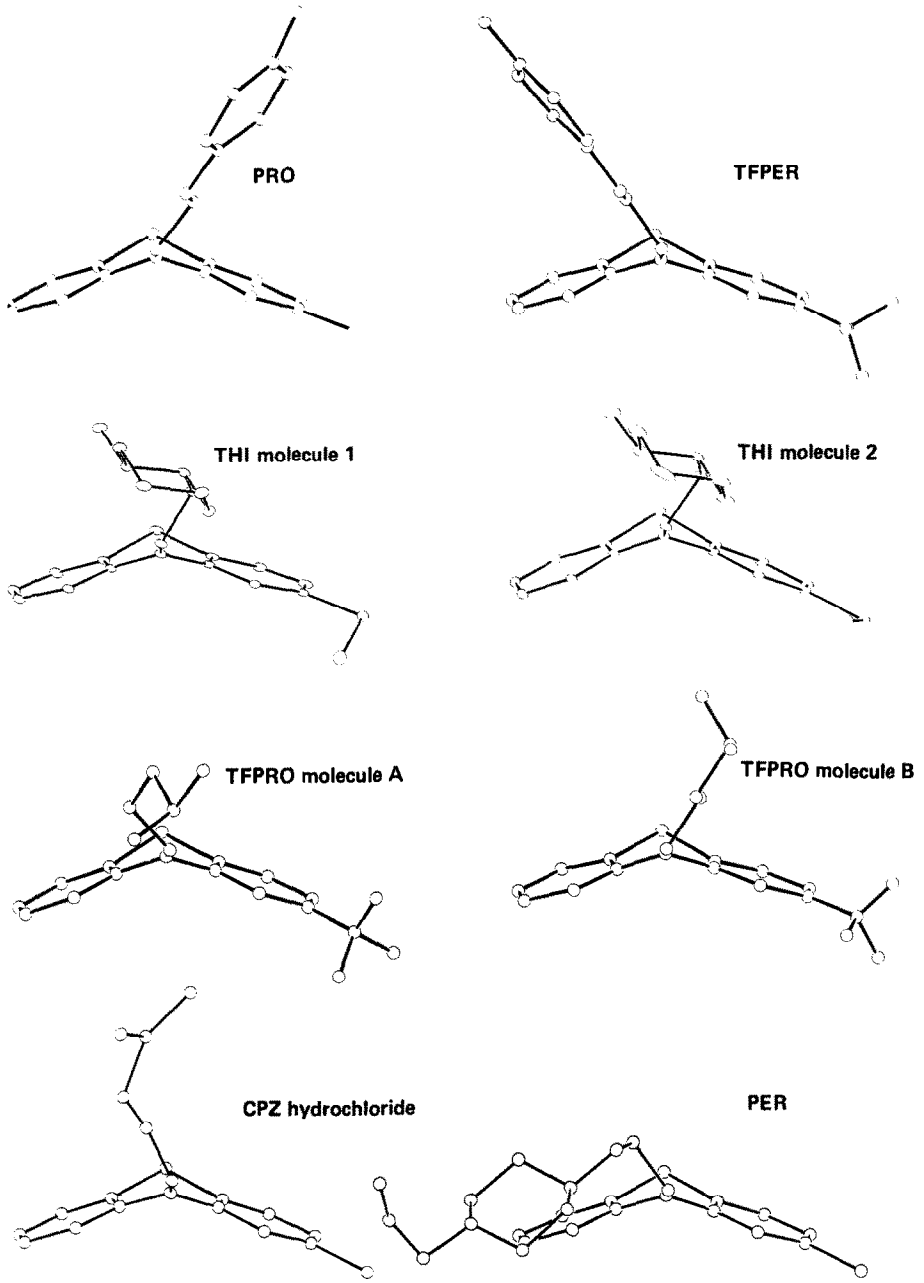

Fig. 4. ORTEP plots of prochlorperazine-methanesulphonic acid (1:2) (PRO), trifluoperazine hydrochloride (TFPER), thioridazine (THI), trifluopromazine hydrochloride (TFPRO), chlorpromazine (CPZ) hydrochloride, and perphenazine (PER). Hydrogen atoms and anions have been omitted for clarity. TFPRO and THI have two independent molecules in the unit cell.

The torsion angles corresponding to No. 1 in Fig. 1 are in the ranges of 64.5–69.4° or 128.7–143.4° in all other psychoactive phenothiazines of which the molecular and crystal structure have been reported, such that the side-chain lies above the ring system when viewed in the same perspective as used in Fig. 3. As illustrated in Fig. 4, this includes perphenazine [38], thioridazine [39], trifluoperazine hydrochloride [40], prochlorperazine-methanesulphonic acid (1:2) [41], chlorpromazine hydrochloride [42], and trifluopromazine hydrochloride [43]. The latter has two independent molecules in the unit cell, with a dihedral angle No. 1 (Fig. 1) of 65° and 145°, respectively.

Four of the structures shown in Fig. 4 were protonated, and protonation itself therefore does not appear to change the preferred conformation from that of the free base. The same was concluded from PILCO calculations with 36 different neuroleptic compounds of various chemical classes [14].

The angle between the planes of the two aryl rings is in the range of 134–146° in the solid state structures of nearly all psychoactive phenothiazine derivatives

[25, 38–43, 44], and does not appear to be correlated with their neuroleptic potency. X-ray diffraction studies have shown that oxidation flattens the ring system in chlorpromazine [45], as observed for CPZSO and DCPZSO. The structures of CPZSO and DCPZSO also have verified the conclusions of a molecular orbital study [36], that a flattening of the ring system to 160° between the aryl rings yields a third conformation of the side-chain with equally low energy, and an opposite orientation in relation to the ring system. The loss of pharmacological activity by sulphoxidation of chlorpromazine and *N*-desmethyl chlorpromazine (the latter is also pharmacologically active [46]) might be due to such a flattening of the thiazine ring by oxidation of the sulphur atom, thus promoting the alternative conformation of the side-chain at the receptor site.

The distance from the terminal N atom at the side-chain to the centre of the substituted benzene ring is closer to a postulated requirement for binding to the α-adrenergic receptor (5.1–5.2 Å) [47], in METSO than in CPZSO and DCPZSO (Table 1). This might suggest an explanation for the relatively high potency of METSO in α1-adrenergic binding, compared to CPZSO and DCPZSO (Table 2). However, these differences in interatomic distances are hardly significant in view of the rotational freedom around bond No. 4 of the side-chain. An inspection of the corresponding interatomic distance in 7-OHCPZ (Table 1), which is much more active in α1-adrenergic binding (Table 2), confirms the statement by Tollenaere *et al.* [18] that the technique of comparing interatomic distances alone and neglecting the three-dimensional aspect of drug–receptor interactions may lead to erroneous conclusions. Protonation of the dimethylamino group, which occurs at physiological pH, must also be expected to influence the distance from the terminal N atom to the ring system.

Although the use of solid state molecular conformations as a key to finding conformations at the receptor site has been rejected by some authors, there have not, to our knowledge, been published IR-spectroscopic, NMR-spectroscopic or other experimental data which have clearly demonstrated a conformation of an antipsychotic drug which is different in solution from that in the solid state. The observation that a series of different phenothiazine metabolites fall into two clearly different conformational categories suggests the existence, not unexpectedly, of fairly well defined energy minima. Furthermore, this suggests the possibility that many of the molecules have similar conformations in solution and in the solid state.

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