Research Article

Molecular Structure and Dynamics of cis(Z)- and trans(E)-Flupenthixol and Clopenthixol

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The three-dimensional structures and molecular electrostatic potentials of the cis(Z) and trans(E)-isomers of flupenthixol and clopenthixol were examined by computer graphics and molecular mechanical calculations, and their internal molecular motions were studied by molecular dynamics simulations \textit{in vacuo} and in aqueous solution. The simulations demonstrated that both the side chains and the tricyclic ring systems of clopenthixol and flupenthixol are highly flexible. The angle between the two phenyl ring planes varied between 105 and 171\degree during the simulations in solution. The electrostatic potentials around the 2-substituent were significantly more negative in the trans(E)-isomers than in the cis(Z)-isomers. The stronger negative potentials may weaken electrostatic receptor interactions and, thereby, cause the trans(E)-isomers to be less active than cis(Z)-isomers. Differences both in three-dimensional structure and in electronic structure may cause the difference in pharmacological activity between cis(Z)- and trans(E)-thioxanthenes.

KEY WORDS: Thioxanthenes; cis(Z)- and trans(E)-isomers; molecular dynamics; conformations; molecular mechanics; electrostatic potentials.

INTRODUCTION

The cis(Z)-isomers of several thioxanthen derivative have antipsychotic effects, while the corresponding trans(E)-isomers are virtually inactive (1,2). The cis(Z)-isomers are much more potent than the trans(E)-isomers in pharmacological tests related to antipsychotic activity (3-5) and in dopamine receptor binding experiments (5,6). Cis(Z)-thioxanthenes show high binding affinities to dopamine D1 and D2 receptors in the brain, and it has been questioned whether their antipsychotic action is mediated mainly via antagonism of central dopamine D2 receptors or by combined effects on D1 and D2 receptors (7).

Thioxanthenes derivatives have a tricyclic ring system which is folded about the central S1-C9 axis (Fig. 1), an electron withdrawing substituent at the 2 position on the tricyclic nucleus, and a side chain with a nitrogen atom separated from the tricyclic nucleus by three carbon atoms. Both flupenthixol and clopenthixol have an N-hydroxyethylpiperazinyl group at the end of the side chain, and their only difference in chemical structure is that flupenthixol has a CF\textsubscript{3} group and clopenthixol a chlorine atom as 2 substituent (Fig. 1). Due to the exocyclic double bond (C9-C16) and the 2 substituent, the thioxanthenes may exist as cis(Z)- and as trans(E)-isomers. The molecular conformation of thioxanthenes may be described by the dihedral angles (D1-D3) of the side chain, the angle (\alpha) between the two phenyl rings, and the distance (d) between nitrogen atom N1 in the side chain (Fig. 1) and the center of the substituted phenyl ring.

The detailed molecular mechanisms of interaction between thioxanthenes and dopamine receptors are not known. Dopamine has a trans extended conformation in crystals (8,9), and it has been suggested that the thioxanthenes mimic the three-dimensional trans conformation of dopamine in their interactions with dopamine receptors (10). Tollenare et al. reported from crystallographic data and PCNO quantum chemical calculations that a good conformational fit could be obtained between trans dopamine and both the active and the inactive isomer of flupenthixol (11). Rebool and Cristau (12,13) compared geometrical parameters in crystal structures of dopamine receptor antagonists and concluded that the compounds had no common preferred conformation. Several other computational and crystallographic studies of dopamine receptor agonists and antagonists have since been performed in order to determine three-dimensional pharmacophoric patterns (14-18).

However, a limitation in the postulated pharmacophoric patterns may have been that previous studies of dopamine receptor ligands have been based upon fairly static concepts of molecular structure. The method of molecular dynamics simulations, which combines a molecular mechanical force field with Newton's equations of motion for a molecular system, has provided new insight into the molecular motions and functioning of biologically active molecules (19-21). This study examines the molecular dynamics, conformations, and molecular electrostatic potentials of the cis(Z)- and trans(E)-isomers of flupenthixol and clopenthixol, by

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Fig. 1. Chemical structure and atom numbering scheme of fluropenthixol. In clopenthixol the CF₃ group is replaced by chlorine atom C11; otherwise similar atom numbers were used. Dihedral angles: D1, C9-C16-C17-C18; D2, C16-C17-C18-N1; D3, C17-C18-N1-C19.

computer graphics and other computational techniques. The main purpose of our study was to explain the differences in pharmacological activities between cis(Z)- and trans(E)-thioxanthenes from their electronic and molecular structures and their molecular dynamics.

METHODS

The subsequent steps of the molecular modeling procedure are shown in Fig. 2. Molecular mechanical geometry optimizations and molecular dynamics simulations were performed with the AMBER 3.0 programs (22–24), using the all atom force field and a 15-Å cutoff radius for nonbonded interactions. A distance-dependent dielectric function \( \varepsilon = r_{ij} / \left( r_{ij} \right)^{6} \) (\( r_{ij} \) : interatomic distance) was used for electrostatic interactions in vacuo, and a constant dielectric function (\( \varepsilon = 1.0 \)) was used for electrostatic energies in the calculations with aqueous solvent. The calculations in vacuo were performed on a DEC VAX 8600/VMS computer. Molecular dynamics simulations in aqueous solution were performed on the VAX 8600 for the first 20 psec and on a Cray X/MP-28 computer for the following 30 psec.

Quantum mechanical atomic point charges were calculated with the QUEST 1.0 program (22,25) on a Cray X/MP-28 computer, using an STO-3G basis set. The QUEST program, which is supplied with the AMBER programs, is an extended GAUSSIAN-80 program (26) that calculates electrostatic potentials over several layers of molecular surfaces by ab initio quantum mechanical methods and projects the potentials into net atomic point charges by an optimization procedure. Electrostatic potentials were calculated over four surface layers 0.2 Å apart, the innermost surface corresponding to 1.4 times the van der Waals radii.

Molecular graphics was done with the MIDAS programs (27–29) on an Evans & Sutherland PS390 workstation with a DEC MicroVAX II/Ultrix system as the host machine. Water-accessible molecular surfaces (30) and electrostatic potentials 1.4 Å outside the surface were calculated with the MIDAS programs, using a 10-Å cutoff radius, and illustrated by color coding of the surfaces.

Molecular Mechanical and Quantum Mechanical Calculations

The AMBER force field did not contain parameters for bond angles and torsion angles around the sulfur atom in the central thioxanthenic ring. The following parameters were used: S–C bond—1.75 Å, 300 kcal mol⁻¹ Å⁻², from the crystal structure of di-p-tolyl sulfide (31); C–S–C angle—98.9°, 62 kcal mol⁻¹ rad⁻², from the microwave spectrum of dimethylsulfide (32); and torsion angle X–C–S–X, where x may be either H or C—1.8 kcal mol⁻¹, twofold barrier. The rotational barrier about the –C–S– torsion angle had previously been determined by quantum mechanical ab initio calculations, using the QUEST program, of the energies of thiophenol with the C–C–S–H torsion angle at different fixed positions (33).

Molecular mechanical energy minimizations were performed by the steepest descent method for 100 cycles, with