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Molecular Structure and Affinity to 5-HT_{1A} Receptor of Chlorophenyl(Piperazinylalkyl)Phthalimides

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X-ray crystallography, quantum-chemical calculations and conformational analysis have been employed to study chlorophenyl(piperazinylalkyl)phthalimides, potential ligands of 5-HT_{1A} receptor. The molecular recognition of investigated compounds by 5-HT_{1A}serotonin receptor has been estimated according to their ability to inhibit the [^{3}H8]-DPAT binding. The model for 5-HT_{1A} pharmacophore has been proposed based on crystal structures of N-(aryl)piperazinyl – alkylphthalimides.

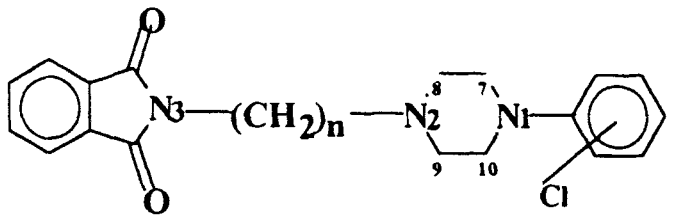
Keywords: psychotropic agents, chlorophenyl(piperazinylalkyl)phtalimides, serotonin receptors, affinity, pharmacophore

The heteroaromatic- or aryl-piperazine derivatives have been widely investigated as potential psychotropic agents. Their neuroleptic and anxiolytic properties result from the interaction with serotonin and dopamine receptors. Mechanism of biological action of these compounds has been related to ligand-receptor self-assembly. To clarify the ligand-receptor mode of interaction it is necessary to determine the electronic and conformational factors that affect recognition and binding processes. Therefore X-ray crystallography, quantum-chemical calculations and conformational analysis have been employed to study chlorophenyl(piperazinylalkyl)phtalimides **I-V**, potential 5-HT_{1A} receptor ligands (Fig. 1). The molecular recognition of the compounds **I-III** has been estimated according to their ability to inhibit the [^{3}H8]-DPAT binding with 5-HT_{1A} serotonin receptor. The K_i values for the compounds **I-III** (5.5, 6.3, 14.0 nM) indicate high affinity of these substances to this receptor.

The Hibert's two-point model [1] of pharmacophore binding to 5-HT_{1A}receptor requires an aromatic ring and a basic nitrogen atom **N2** placed ca. 5.2–5.6 Å from the aromatic ring centroid. The pharmacophores for agonist and antagonist binding sites differ in the out-of-plane displacements of the basic nitrogen atom from the aromatic ring which should have the value of 0.2 Å in the agonists and ca. 1.6 Å in the antagonists.

All studied molecules **I-V**, for which structures have been determined by X-ray analysis, show the distance of the basic nitrogen atom to the aryl nucleus in the range 5.6–6.2 Å and the out-of-plane displacements of the nitrogen atom in the range 0.5–0.7 Å. All molecules are in the

* Author for correspondence.



I. n=4, o-Cl
II. n=5, o-Cl
III. n=6, o-Cl
IV. n=6, p-Cl
V. n=4, p-Cl

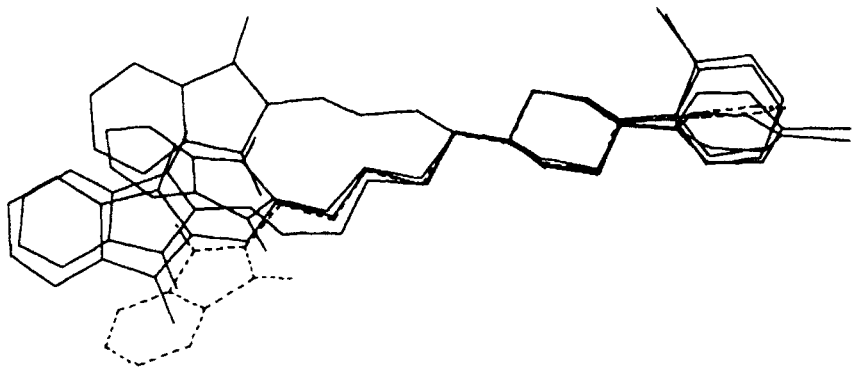
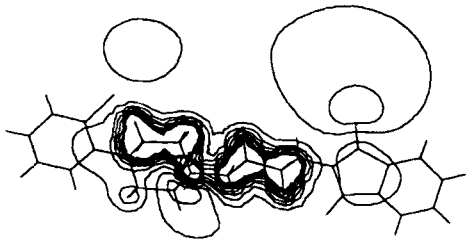


FIGURE 1 Superposition of molecular conformations observed in crystals for compounds I – V

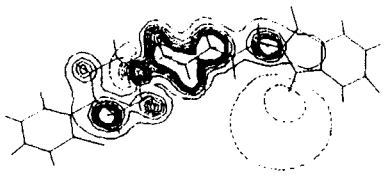
fully-extended conformation. Thus, structural and conformational requirements for agonist ligands of 5-HT_{1A} receptor are fulfilled by the molecules **I-V**. Conformational analysis of **I-V** showed that the rotation around single bonds in alkyl spacer can lead to a claw-like shape of the molecule. This brings the basic nitrogen atom close (4.2–6.5 Å) to another lipophylic part of the molecule – to the phthalimide fragment centroid. These results agree with the data reported in [2], where for the similar compounds the claw-like conformation was proposed in solution based on NMR measurements. In the fully-extended conformations observed in crystals the distances between the basic N2 atom and the phthalimide fragment are much longer (8.7–9.2Å).

The high occupied molecular orbital which characterises the donor properties of the molecules **I-V** are determined mainly by the **N1** atom p_π-orbital and the phenyl ring p_π-orbitals what is in line with Humbert's [3] model of aromatic ring binding site. The interaction sites can be conveniently characterised with the aid of the molecular electrostatic potential (MEP) [4]. For molecules **I-V** the MEP (Fig. 2) is localised in the region of carbonyl oxygen atoms of the phthalimide fragment and in the region of phenyl and piperazine rings.

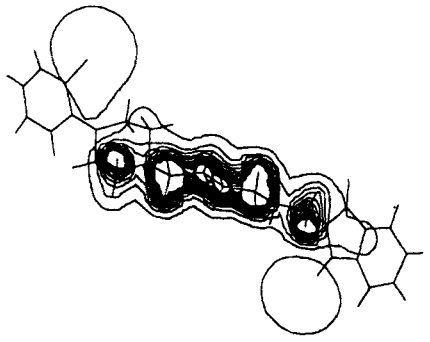
Taking into account the gathered information about the structure of N-(aryl)piperazinylalkylphthalimides we felt that the model for 5-HT_{1A} pharmacophore requires some reconsideration which would include the following facts:



I



II



III

FIGURE 2 Distribution of MEP for compounds **I-III**

1. all important binding sites of N-(aryl)piperazinyl-alkylphthalimides have to be included in structural parameters describing the model for $5HT_{1A}$ pharmacophore,
2. the proposed model should be independent on the length of alkyl spacer.

The following parameters satisfy the above-mentioned requirements (Fig. 3):

1) $\Delta_1 = |d1 - d2|$,

where d1 is the distance between the phenyl ring centroid and (N1C7C10) fragment and d2 is the distance between the phthalimide centroid and (N1C7C10) fragment.

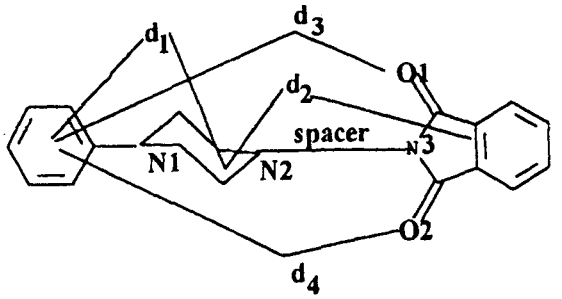


FIGURE 3 Scheme for $5\text{-}HT_{1A}$ pharmacophore model

2) $\Delta_2 = |d3\text{-}d4|$,

where d3 and d4 are the distances between the centre of phenyl ring and oxygen atoms O1 and O2 respectively.

For compounds **I-III**, showing high affinity to the $5\text{-}HT_{1A}$receptor, Δ_1 and Δ_2 values are in the range 3.86–6.42Å and 0.16–1.90 Å, respectively. For inactive N-(aryl)piperazinyl-alkylphthalimides derivatives [5,6] the corresponding values are 0.477, 3.035 Å and 2.017, 2.018 Å, respectively. Thus we could assume that for ligands with significant affinity to $5\text{-}HT_{1A}$ receptors the values of Δ_1 and Δ_2 satisfy the following conditions:

$$\Delta_1 > 3.8 \text{ Å and } \Delta_2 < 2.0 \text{ Å}.$$

Acknowledgements

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