In 2005, the World Health Organization concluded, among other things, that: (1) The world impact of mental disorders on the quality of life is superior than that of chronic diseases such as arthritis, diabetes or heart and respiratory diseases; and (2) It is expected that by 2020, depression will be the number one disease in the developed world. The pharmacological treatment of these conditions with antidepressant is effective in approximately 60% of the patients. Typical antipsychotics, also called neuroleptics, are a group of drugs with a very heterogeneous chemical nature but with a common mechanism of action. They act primarily by blocking dopamine D_2 receptors. In the group of neuroleptics derived from phenothiazine, for example, the side chain has always 3 carbon atoms followed by a $-NR_2$ group, which is essential for antipsychotic the properties. The substitution for a chlorine in the phenothiazine core induces asymmetry, which increases the pharmacological action. A $-CF_3$ group in the same position further enhances the antipsychotic and antiemetic actions of phenothiazines. Compared to CPZ, fluphenazine is approximately 20 times more potent and tioproperazine 10 times. Thioridazine, however, has only half of the pharmacological activity of CPZ. Thioxanthenes, such as chlorprothixene, have cis / trans isomerism. The cis- isomer has a higher potency than the trans- isomer and induces more phototoxicity. Furthermore, less potent drugs contain a piperidine group in the side chain.

All antidepressants are equally effective for the short term treatment of acute depressive symptoms, but differ in their adverse effects. For example, all drugs with electron-attracting substituents on the ring system are good antipsychotics, but induce more phototoxicity. Photosensitivity is an abnormal skin reaction that occurs by the combination of a chemical and exposure to ultraviolet light (UVA). The general mechanism for this phenomenon is not known, but it is postulated that the photosensitizing agent absorbs energy and its triplet state interacts directly with cellular components. Recent reports indicate that the new antidepressants are only marginally more effective than a placebo. The results of the investigation with "old generation" tricyclic antidepressants, however, indicate that the interaction of biomolecules with the excited state of these drugs may be one of the steps in the aforementioned mechanism. Therefore, understanding the properties of these excited states and their subsequent reactions will enable the development of more selective and more effective drugs with fewer side effects. For this purpose, the main objective of this work is to use

chlorprothixene and levomepromazine as model for the study of the photophysics and photochemistry of enantiomeric drugs, in order to determine their mechanism of phototoxicity.

In this work we demonstrate that the high power laser flash photolysis (LFP) of chlorprothixene (zCPTX) produces P-type delayed fluorescence and a short-lived intermediate absorbing at 360 nm with a lifetime of about 56 ns under anaerobic conditions. The photochemistry zCPTX and zCPTX-HCl depends on the microenvironment (solvent, oxygen concentration, pH, irradiation wavelength, etc.). It was also demonstrated that the solvents determine the extent of the zCPTX photodegradation and the distribution of photoproducts, as well. The formation of its main product, chlorothioxanthone (CTX), is not dependent on the concentration of dissolved oxygen, but - instead - it is favored in anaerobic environments and in the presence of water. Besides, depending on the solvent, the formation of CTX requires that the alkylamino group at the position 9 of the thioxanthene to posses a nitrogen free electron pair.

The results obtained for the photophysical study of CTX clearly demonstrate that the intersystem crossing quantum yield decreases a lot with an increasing hydroxility of the media. Although that quantum yield decreases a lot, its lifetime increases drastically. This property is very important, because the carbonyl group of CTX in the triplet state has a considerable photoreactive character. It can act as an electrophilic radical capable of abstracting hydrogen atoms from any biomolecules, resulting in a phototoxic or photoallergic response.

In the study levomepromazine (LPZ), it was demonstrated that the formation of the main product, levomepromazine sulfoxide (LPZSO), is not obtained from the production of singlet oxygen, as previously proposed by other authors. Actually, LPZSO is obtained by the formation of the radical cation of LPZ, which is produced by an electron transfer between the triplet state and molecular oxygen. This work also demonstrates that the processes of electronic energy transfer between the triplet state of LPZ and molecular oxygen are determined by the solvent, which implies that its photochemistry is also depends on these parameters. Based on these data, a general mechanism for the formation of LPZSO in PBS is formulated.