Summary

In this thesis various pharmacological investigations performed with N-0437 are described.

Chapter I is an introduction to the experimental chapters of this thesis. It deals with the role of dopamine in the brain, the diseases in which dopamine is involved, classifications of the dopamine receptor and it provides a review of the most selective dopamine agonists and antagonists.

Chapter II contains a short description of the test models which have been used in the experimental chapters III t/m IX. In the latter chapters these test models are therefore only briefly mentioned. This chapter also contains the most recent views on the involvement of D-1 and D-2 receptors in the pharmacological test systems. Moreover the synthesis of N-0437 is described.

Chapter III is a study, containing a comparison between N-0437 and two analogues, N-0434 and N-0734. The test models used are mainly in vivo test models for potency and selectivity. Behavioural as well as biochemical studies are described. The most interesting results of this chapter are the high oral activity and the long duration of action of N-0437.

Chapter IV deals with the in vitro activity of tritium-labelled N-0437. ^{3}H-N-0437 appeared also in vitro to be a very potent dopamine agonist, which was selective for D-2 receptors. Dopamine agonists and antagonists with D-2 activity are potent displacers, whilst drugs belonging to various other pharmacological classes appear to be very poor ones.

Chapter V is an in vitro study on the effects of chemical lesions and the influence of metal ions and GTP on the binding of ^{3}H-N-0437 to D-2 receptors. From the lesion experiments it became clear that ^{3}H-N-0437 preferentially binds to postsynaptic dopamine receptors. GTP and Na^{+} are able to decrease the specific binding of ^{3}H-N-0437 while Hg^{++} completely nullified the binding.

Chapter VI is a study performed in collaboration with other laboratories. It deals about the potency and selectivity of racemic N-0437 for dopamine receptors. N-0437 was tested for a possible discrimination between pre- and postsynaptic dopamine receptors in

vivo as well as in vitro, and in addition for possible serotonergic activity in vivo. It appeared that racemic N-0437 does not discriminate between the pre- and postsynaptic receptors and in addition showed no serotonergic activity in vivo. In this study we also tested the in vitro affinity of racemic N-0437 for various non-dopaminergic receptors. It appeared that N-0437 was about 280 times more selective for D-2 receptors than for α_2-adrenergic receptors. For other kinds of receptors the selectivity ratio was many more times bigger.

Chapter VII describes an in vitro autoradiographic study with ^{3}H-N-0437. This work was performed in the research laboratory of Sandoz in Basel. Because of the low non-specific binding of ^{3}H-N-0437, this compound appears to be an excellent radioligand to visualize the D-2 receptors in the brain. The pharmacological profile and saturability obtained with autoradiography were in very good agreement with the in vitro radioligand binding studies described in chapter IV.

Chapter VIII This chapter deals with certain molecular properties of the DA receptor. It has been described in literature that dopamine antagonists are able to protect dopamine receptors against N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) induced receptor inactivation. It has also been reported that dopamine agonists and antagonists bind to different binding sites. Because of the selectivity of N-0437, this compound was tested for its possible protecting capacity. In contrast to dopamine antagonists, N-0437 was not able to protect the dopamine D-2 receptor against EEDQ induced inactivation.

Chapter IX In the latter stages of this research project racemic N-0437 was resolved into the (+) and (-) enantiomers. These optical antipodes were examined in test models for pre- and postsynaptic dopaminergic activity. It appeared that the (+) enantiomer a is very selective presynaptic agonist and a postsynaptic antagonist, while the (-) enantiomer is a full agonist and labels both pre- and postsynaptic receptors.These properties are of importance for therapeutic application.

From the above studies it can be concluded that N-0437 is a very potent and selective dopamine D-2 receptor agonist. Racemic N-0437 is capable of stimulating both pre- and postsynaptic receptors. The (+) enantiomer is a partial dopamine agonist, whereas the (-) enantiomer is a full agonist. Because of its potency and selectivity, high oral

activity and long duration of action, this compound is a very promising candidate for therapeutic use. The (+) enantiomer could have an application for the treatment of schizophrenia as it stimulates in very low concentrations presynaptic dopamine receptors. The (-) enantiomer is, because of its potency on postsynaptic receptors, is a very promising drug for Parkinson's disease.