

Summary

The main interest of our research group is the medicinal chemistry of agonists and antagonists of the neurotransmitters dopamine (DA) and serotonin (5-HT) and their modes of pharmacological interaction with dopaminergic and serotonergic neurotransmitter systems in the brain. The group is currently interested in the rational design, synthesis and pharmacological evaluation of new dopaminergic and serotonergic agents with clinical potential.

Dopamine is an important neurotransmitter in the brain and is known to play an important role in Parkinson's disease, schizophrenia, and possibly depression. Serotonin is thought to be involved in various functions such as anxiety, aggression, depression, stress, sexual behaviour, and body temperature.

Chapters 1 and 2 give the background information for chapters 3-9. Chapter 1 is divided into three parts. The first part gives an introduction about G-protein coupled receptors. It illustrates that those receptors that interact with G-proteins share a variety of structural and functional similarities. The second part deals with dopamine, the dopaminergic system, related pathology and the classification of the dopamine receptors. Part three deals with the serotonergic system in the same way.

Chapter 2 contains a review of the structure-activity relationships (SAR) of dopaminergic and serotonergic agonists and antagonists, with the emphasis on 2-aminotetralins and related tricyclic compounds. The receptor concept of McDermed, the basis for the development of almost all the compounds synthesized in this thesis, is briefly described and compared with some other models reported in the literature.

In chapter 3 the synthesis of a series of 2-(N-methyl-N-propargylamino)tetralins is described, which are studied with respect to their dopamine agonist and monoamine oxidase inhibitory activities. It was concluded that the mono and dihydroxylated compounds have MAO inhibiting and dopamine receptor stimulating activities. The MAO inhibitory activity predominates in the monohydroxy structures, whereas the dopamine agonistic effect is predominant in the catecholic compounds.

Chapter 4 describes the synthesis and pharmacological activity of the N-methyl-N-propargyl analogue of the potent 5-HT_{1A} agonist 8-OH-DPAT. The results demonstrate that the compound has a high affinity for the 5-HT_{1A} receptor. The compound is a 5-HT_{1A} agonist, as well as an irreversible inhibitor of MAO-A, and may be useful for the treatment of disorders of the central nervous system, especially those related to the serotonergic system.

The synthesis of the 4-propylhexahydronaphthoxazines is described in chapter 5. From the pharmacological data in this study it can be concluded that the

naphthoxazines, and in particular the 9-hydroxy isomer, possess not only a very high affinity for the DA D₂ receptor but are also very selective for this receptor subtype.

In chapter 6 the resolution of 4-propyl-9-hydroxynaphthoxazine (PHNO) is described. A single crystallization of the diastereomeric salts, obtained with the enantiomers of phencyphos and chlocyphos, yielded optically pure products. The effects of the enantiomers on the dopaminergic striatal system, studied by means of *in vivo* microdialysis in freely moving rats, proved that the activity mainly resided in the (+)-enantiomer. (-)-PHNO displayed only a weak DA agonistic activity at higher doses.

Chapter 7 describes the 9-steps synthesis of some tetrahydrobenzopyranoxazines. The activities of these compounds were evaluated *in vivo* and *in vitro*. In all the test models, the compounds give a low response. However, the 9-hydroxy isomer was found to display presynaptic activity in the brain microdialysis model. This chapter also focuses on the importance of pK_a values for central dopamine receptor activation. It was shown that a correlation exists between the pK_a value of the nitrogen atom and the biological activity at the dopamine receptor. The conclusion is that the protonated form of the dopamine agonists is the active species at the dopamine receptor. Our results indicate that diminishing the intrinsic activity by lowering the pK_a value of the nitrogen atom might be a method to increase the selectivity for DA autoreceptors.

Chapter 8 describes a very useful reaction for the para chlorination of some 5-hydroxy-2-(dialkylamino)tetralins. The regioselectivity in these chlorination reactions was excellent but unexpected. Scope and limitations of this reaction are discussed and a plausible reaction mechanism is given.

The results of the study in Chapter 9 show that substitution of chlorine in the phenyl ring of the 2-aminotetralins has much influence on the activity and selectivity of the test compounds. Substitution of chlorine in the 8-position resulted in compounds with a decreased affinity for D₁ and D₂ receptors. The non-chlorinated and chlorinated 2-aminotetralins, were also studied in the brain microdialysis and in the 6-hydroxydopamine (6-OHDA) models. Chlorination resulted in compounds with a greatly decreased agonistic activity for pre- and postsynaptic dopamine receptors. The effect is most dramatic in N-0434, in which chlorination gives a compound with DA antagonistic properties. Surprising is also the high affinity of the chlorinated compounds for the 5-HT_{1A} receptor, indicating that a small modification within these molecules gives compounds with affinities for another G-protein coupled receptor.

It can be concluded from these investigations that subtle changes in the structures of the compounds tested in this thesis have a large effect on the activity and selectivity for different receptors/receptor subtypes.