Parkinson’s disease (PD) is a progressive neurodegenerative disorder that affects 1-2% of the population over 65 years of age. When the disease is manifest, a large proportion (70–80%) of dopaminergic neurons in the substantia nigra pars compact (SNc) have already been lost, resulting in reduced dopamine (DA) synthesis and release from the striatal nerve terminals. The dopaminergic neurons are responsible for the normal functioning of the human motor system and the dysfunction of dopaminergic neurons causes tremor, bradykinesia, hypokinesia, balance and gait disturbances, which are the main symptoms of PD. The pathogenesis of PD is mostly likely multi-functional and various processes, such as mitochondrial effects, glutamate toxicity genetic factors and oxidative stress.

Treatment aims in PD include the provision of symptomatic relief, reduction of functional disability, halting or slowing of the neurodegenerative process and the prevention of long-term complications by proper initiation of therapy. Anticholinergic agents and amantadine are used primarily as initial symptomatic therapy for PD, but their usefulness is limited by adverse effects, especially in the elderly, and by the availability of more effective approaches. In 1967, L-dopa was started to use clinically and PD management had greatly improved. However, dyskinis and adverse effects have reduced the impact of L-dopa therapy. The co-administration of L-dopa with aromatic amino acid decarboxylase (AADC) inhibitors or peripheral catechol-O-methyl transferase (COMT) inhibitors potentates and extends the effect of L-dopa. Monoamine oxidase (MAO-B) inhibitors are used as add-on to L-dopa as well. Early treatment with Selegiline®, a well known MAO-B inhibitor, delays the need for initiation with L-dopa therapy. It must be noted that L-dopa therapy is started mostly only when all other available drugs have lost their efficiency, since L-dopa has marked side effects after long term use.

Although L-dopa remains the “drug of choice” in treating PD, other anti-Parkinson agents have proven beneficial when L-dopa is contraindicated. Apomorphine, a potent DA agonist, is useful as a “rescue” during the “off” periods of severely disabled patients who have received L-dopa. However, the high first-pass effect, poor oral bioavailability and induced adverse effects with apomorphine limited its application. Both L-dopa and
Summary

Apomorphine have a catecholamine moiety, which hampers the passage of the blood brain barrier. However, as an amino acid, L-dopa can be transferred into brain by transporters.

An alternative approach to the treatment of PD is starting with DA agonists, such as bromocriptine and pergolide. These DA agonists have shown to be helpful in the treatment of PD both as monotherapy and as adjunctive treatment with L-dopa. DA agonists are less likely to cause dyskinetic side effects comparing to L-dopa, but still induce adverse effects, including nausea, vomiting, postural hypotension, confusion, and visual hallucinations.

In many years, different kinds of DA agonists have been investigated and some of them have a catecholamine moiety. Although many efforts have been made to overcome the bioavailability of the catecholamine, there are few drugs with catechol moiety on the market. PD-148903 was found by chance. It is an enone that is inactive in vitro, but converted in vivo to a catecholamine that shows pronounced DA agonist activity. This kind of compound is described as prodrug. Prodrugs are compounds which are pharmacologically inactive by themselves but converted in vivo to the active forms, requiring spontaneous or enzymatic transformation within the body. Prodrugs are designed to overcome pharmaceutically and/or pharmaco-kinetically disadvantages of the parent drug molecules, such as limited bioavailability, duration, etc.

This thesis describes the research of a series of enone prodrugs. For comparison, the corresponding catecholamines of these enone prodrugs were also synthesized and pharmacologically evaluated.

Chapter 2 describes a [g]quinoline enone that acts as a potent prodrug of a DA agonist. The synthesis of this compound (GMC-6650) was attempted from different routes. The resolution of the racemic compound was performed by chiral preparative HPLC, consequent X-ray analysis elucidated that the absolute configuration of the active enantiomer is (R, R)(–). The microdialysis data demonstrated a strong decrease of DA release after 10 nmol/kg po. The serum and brain samples were analyzed and the corresponding catecholamine of active enantiomer (–)-GMC-6650 were found in both samples. The catecholamine of the inactive enantiomer (+)-GMC-6650 was found only in blood, not in brain. Therefore, it can be concluded that there were no catecholamine formed in brain after the enantiomer (+)-GMC-6650 was given to rats. The long duration and po potency makes GMC-6650 an interesting candidate for the treatment of PD.
Chapter 3 described the synthesis and pharmacology of the catecholamine TL-334, which is the in vivo active form of GMC-6650. This DA agonist was known for decades, but not much pharmacology was done on this potent DA agonist. A novel synthetic route of this compound was described in this chapter. The microdialysis study revealed that it is a very potent DA agonist, since a low dose, 10 nmol/kg sc decreases the release of DA to 40% of basal value for more than 6 h. Although after po administration this compound is not potent as GMC-6650, it is still 100 times more potent than apomorphine. This property makes this compound a candidate of DA agonist for PD as well.

In Chapter 4 we extended the enone concept to benzo[f]quinoline catecholamine (1.27d), which was known as a DA agonist for years. The benzo[f]quinoline enone 4.1a and its corresponding catecholamine 1.27d were synthesized and pharmacologically evaluated. Comparing to GMC-6650, 4.1a is less potent, since its corresponding catecholamine is less potent than the catecholamine (TL-334) as well, which is formed from GMC-6650 in vivo. The microdialysis of 4.1a displays a significant decrease of DA levels. Therefore, 4.1a seems a good candidate for the treatment of PD.

Chapter 5 described the synthesis of apo-enone, which is the corresponding enone of apomorphine. Although it is logical to prepare this compound, its very instable character makes it unlikely to be developed to become a drug. The alkyl analog of apo-enone (with propyl group instead of methyl group) showed a higher stability, which made it possible to obtain an enantiomer for X-ray analysis. The X-ray analysis supports the hypothesis that the driving force for this instability is probably the presence of torsional strain in these enones, resulting in aromatization of the middle ring.

Chapter 6 described a new prodrug of apomorphine: mono-pivaloyl apomorphine. There have been various ester prodrugs of apomorphine synthesized to increase the bioavailability of apomorphine. However, all the known compounds are di-ester-apomorphine, such as: di-acetyl, di-propionyl, di-butyryl, di-iso-butyryl, di-pivaloyl, etc. Since the bulky groups causes a delay in the hydrolysis of apomorphine, the use of a mono-pivaloyl apomorphine ester might improve the bioavailability. Therefore, mono-pivaloyl apomorphine was synthesized and pharmacologically evaluated. It is evident that mono-pivaloyl apomorphine has a much longer duration of action than apomorphine itself.
In summary, in this thesis, the chemical synthesis as well as the pharmacology evaluation of a series of enone prodrugs and their corresponding catecholamines were described. Several prodrugs compounds, when evaluated with microdialysis, showed an improved bioavailability when compared with the parent compound. In addition a mono-pivaloyl ester of apomorphine was investigated that displayed better pharmacokinetic properties than apomorphine itself.