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Letters

A New Type of Prodrug of Catecholamines: An Opportunity to Improve the Treatment of Parkinson's Disease

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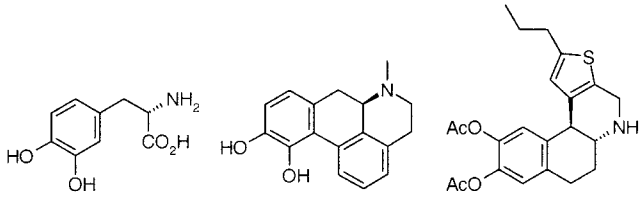
Abstract: After decades of research around dopamine agonists, we have found a promising compound in S-PD148903 that represents a new type of prodrug, which in the rat is bioactivated to the catecholamine S-5,6-diOH-DPAT, known to display mixed dopamine D_1/D_2 receptor agonist properties just like apomorphine. This prodrug has an enone structure which by an oxidative bioactivation mechanism is converted to the corresponding catechol and is delivered enantioselectively into the CNS. This novel concept has the potential to revolutionize the treatment of Parkinson's disease by competing with L-DOPA, the current treatment of choice.

Introduction. About 40 years ago, Arvid Carlsson (Nobel Prize laureate in medicine 2000) suggested that L-DOPA would constitute a possible therapy for Parkinson's disease (Chart 1).[1,2] L-DOPA is a prodrug, which delivers dopamine (DA) to the DA deficient parts of the Parkinsonian brain. Still today, L-DOPA is the treatment of choice for this neurodegenerative disease, despite the fact that several dopamine receptor agonists have been developed through the years.[3,4] Most of these are DA D_2 receptor agonists (e.g., bromocriptine, pergolide, pramipexole, and ropinirole). Another is apomorphine that is a mixed DA D_1/D_2 agonist like DA itself.[5] It has been shown that the D_1/D_2 effect synergistically stimulates locomotor activity in rats.[6] This makes apomorphine more efficient than the D_2 agonists in this respect, and it is a fact that apomorphine has a very beneficial anti-Parkinson effect, especially in L-DOPA resistant patients in the on/off stage of the disease.[7]

Chart 1. Molecular Structures of L-DOPA, Apomorphine, and ABT-431



Unfortunately, the oral bioavailability of apomorphine is very low. So far, the only acceptable routes of administration for apomorphine for Parkinson's disease are subcutaneous infusion via a pump system and subcutaneous injections. Transdermal delivery systems of apomorphine have also been tried but with little success so far.[7] It is thus very likely that an orally active DA D_1/D_2 agonist, mimicking the pharmacological and clinical effects of apomorphine, would be a fierce competitor to L-DOPA for the treatment of Parkinson's disease. The novel enone prodrug S-PD148903 or one of its analogues could meet these criteria.[8]

Several types of catecholamine based prodrugs of DA, aporphines, and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) have been reported.[9−11] Commonly, these ester or carbamate derivatives of the active principle do not give sufficient improvement over the drug itself.[12] Recently, a diacetyl ester prodrug of a catecholamine (ABT-431) proved to have efficacy in treatment of Parkinson's disease—however, only after intravenous administration.[13,14]

Synthesis. The two-step synthesis of PD148903, isolation and resolution, to give (−)-PD148903 and (+)-PD148903 are remarkably simple (Scheme 1).[8,15,16] A

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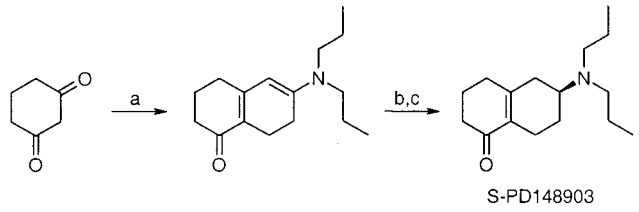
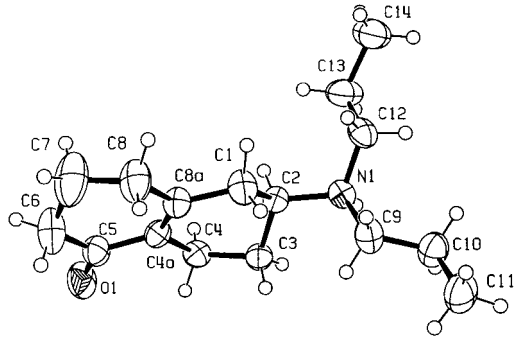
Scheme 1[a]



[a] Reagents and conditions: (a) $(CH_2O)_n$, Pr_2NH, acetone, toluene, 85 °C, 3 h; (b) $NaBH_3CN$, THF, AcOH, 0 °C, overnight; (c) (*S*)-ditoluyltartaric acid, *i*-PrOAc.

Chart 2. Molecular Conformation and Atom Numbering Scheme of S-PD148903



Mannich type reaction generates an intermediate structure that, without purification, is reduced to racemic PD148903. The desired active enantiomer is crystallized from the reaction mixture using enantiomerically pure ditoluyltartaric acid. Resolution is accomplished by recrystallizing this salt. Single-crystal X-ray analysis of the pure (−)-PD148903 hydrochloride showed it to have an 'S' absolute configuration (Chart 2). Synthesis simplicity and speed outweigh the low chemical yields of these reactions.

Pharmacology. In vitro, the racemic prodrug (PD148903) has no binding affinity for the DA receptor family. However, biochemical and behavioral experiments in vivo proved that the prodrug is converted to a DA agonist.[8,15,16] We studied the pharmacological effects of the separated enantiomers by measuring their effects on the endogenous DA levels in the corpus striatum, the brain area of interest in Parkinson's disease, using microdialysis in freely moving rats.[17,18] Because microdialysis is a presynaptic model to investigate the pharmacological effect of a DA agonist, it is expressed as a decrease of the endogenous DA levels. For S-PD148903, a significant decrease of 50% and 70% of control values was observed after administration of 0.4 and 1.2 μmol kg^{-1} po, respectively (Figure 1). From 15 min post-administration until the end of the experiment, at both doses, endogenous DA levels were strongly and significantly decreased, demonstrating a potent and long-lasting pharmacological effect. Figure 1 also shows that R-PD148903 was inactive at a dose of 1.2 μmol kg^{-1} sc.

The postsynaptic effect of orally administered S-PD148903 was studied in the Ungerstedt rat model for Parkinson's disease.[19] In this model, induction of contralateral rotations is a sign that the compound tested is able to alleviate Parkinsonian symptoms. Thus, unilaterally 6-OH-DA lesioned male Wistar rats repeatedly received S-PD148903 by administration of 0.1 μmol kg^{-1} sc or 1.0 μmol kg^{-1} po. At both doses, S-PD148903 induced contralateral turning behavior until the end of the experiment after 3 h giving similar results (Figure 2). Though large individual differences were observed in response to treatment, the individual response did not change significantly upon repeated testing. Saline experiments were not included as no effect was observed at all.

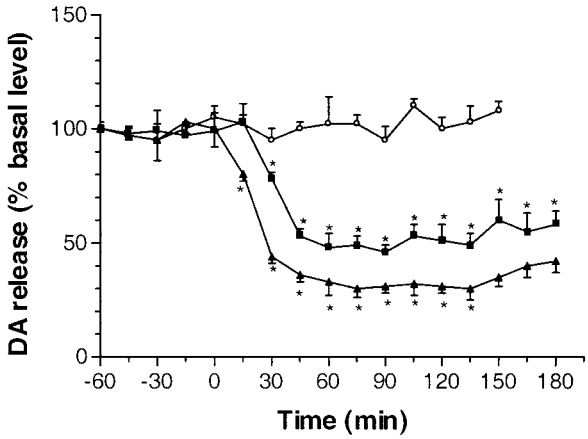


Figure 1. Effect of S-PD148903 (0.4 and 1.2 μmol kg^{-1} po, ■ and ▲, respectively) and R-PD148903 (1.2 μmol kg^{-1} sc, ○) on striatal DA release in freely moving rats. The results are the mean (±SEM) of data obtained from four rats (*p < 0.05).

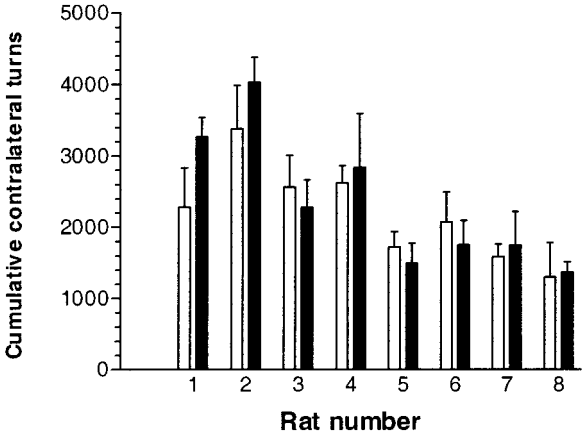
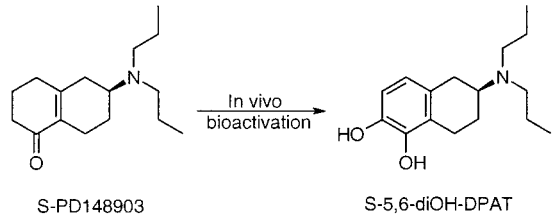


Figure 2. Contralateral rotations in unilaterally 6-OH-DA lesioned rats induced by S-PD148903 dosed at 1.0 μmol kg^{-1} po (white) and 0.1 μmol kg^{-1} sc (solid). Each bar is the average (±SEM) of three tests. The mean cumulative contralateral rotations (±SEM) of all rats tested were 2190 ± 180 (po) and 2429 ± 252 (sc).

Metabolite Identification. On the basis of structural similarity, conversion of the prodrug to one or more dopaminergic, hydroxylated aminotetralins was hypothesized. This was tested by administering 35 μmol kg^{-1} of S-PD148903 sc to male Wistar rats in a striatal microdialysis experiment. The presence of 5,6-di-OH-DPAT in the dialysate was deduced by comparison of the HPLC retention time of an electrochemically active eluting peak with that of an authentic sample. This formation of 5,6-di-OH-DPAT was observed in the striatum, coinciding with a typical dopaminergic behavioral syndrome.[20] The identity of the active metabolite as being 5,6-di-OH-DPAT is further supported by recent HPLC/MS/MS analyses of blood and brain samples after the administration of S-PD148903.[16] Since S-PD148903 has the same absolute configuration as the

Scheme 2. In Vivo Bioactivation of S-PD148903 to S-5,6-diOH-DPAT



pharmacologically active enantiomer of 5,6-diOH-DPAT, it is likely that the metabolite observed is S-5,6-diOH-DPAT (Scheme 2). The striatal presence of 5,6-diOH-DPAT was only detected after the administration of the in vivo active prodrug enantiomer, S-PD148903. Even after administration of 350 μmol kg^{-1} of R-PD148903 sc, no 5,6-diOH-DPAT could be detected in the striatum.

Conclusion. A novel type of orally active prodrug of a potent dopaminergic catecholamine was discovered. Pharmacological evaluation of S-PD148903 in striatal microdialysis showed a rapid onset of action after oral administration and a long duration of action. The striatal presence of a catecholamine was observed only after administration of S-PD148903, indicating an enantioselective bioactivation of S-PD148903 or an enantioselective delivery of the catecholamine. Since we previously reported some close analogues of PD148903 that also induced dopaminergic behavior in vivo, bioactivation to a hydroxylated aminotetralin may be a general feature of this type of compounds.[8] Since S-PD148903 is effective in a rat model of Parkinson's disease, S-PD148903 or one of its analogues could be of use in the treatment of Parkinson's disease.

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Supporting Information Available: Preparation of S-PD148903, dosing, sampling, analysis, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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