Chapter 4

Oxime derivatives of PD217015 and PD148903. Orally active anti-Parkinson cascade prodrugs

ABSTRACT

A series of oxime ether and oxime ester derivatives of the potential anti-Parkinson prodrug PD148903 (2.3) were synthesized and evaluated in pharmacological models. Oximes 4.3 (hydroxyl-oxime) and 4.4 (methoxyl-oxime) were inactive in vitro but in the Ungerstedt rat model for Parkinson’s disease 4.3 and 4.4 produced a pronounced and long lasting effect at 1.0 mg kg\(^{-1}\) po. Enantiomerically pure (−)-4.3 and (−)-4.10 (acetyl-oxime) were prepared from 2.3a (= (−)-2.3) and produced a potent effect at 0.3 mg kg\(^{-1}\) po. Large individual differences were observed in responsiveness between rats. The tosylated oxime (4.14) was found inactive up to 10 mg kg\(^{-1}\) po. Though less potent than 2.3 itself, oxime derivatives of 2.3 can be orally active, most likely acting as cascade prodrugs.
4.1 INTRODUCTION

In chapters 2 and 3, the synthesis and pharmacological evaluation of the orally active prodrug 2.3, its most active enantiomer, 2.3a and some analogs were discussed.\textsuperscript{1} These prodrugs were found to be highly efficacious and to have a long lasting effect in the Ungerstedt rat model for Parkinson’s disease. Pharmacologically active enone prodrugs that were investigated so far are considered to be rapidly bioactivated in two steps to their biologically active catecholamine counterparts. Bioactivation of 2.3 proved to be selective for the (S)-(−)-enantiomer and the biologically active metabolite, the mixed DA D\textsubscript{1}/D\textsubscript{2} agonist (S)-5,6-dihydroxy-2-(N,N-di-n-propylamino)tetralin ((S)-5,6-di-OH-DPAT, (S)-2.10), was delivered enantioselectively into the CNS (Scheme 4.1).\textsuperscript{2}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme4_1.png}
\end{center}

\textbf{Scheme 4.1} Bioactivation of PD217015 (2.3a) to (S)-5,6-di-OH-DPAT ((S)-2.10).

In the Ungerstedt rat model for Parkinson’s disease, the pharmacological profiles of 2.3a and (S)-2.10 were similar at a dose of 0.1 mg kg\textsuperscript{-1} po (Chapter 2, Figure 2.5). An equally rapid onset of action was observed followed by a maximal effect of both compounds varying from 1 to 3 h, followed by a gradual decrease in activity. Rapid bioconversion of 2.3a to (S)-2.10 might be forcing the pharmacological profile of the prodrug to follow that of the catecholamine drug.

To obtain a more constant pharmacological effect and a longer duration of action it was thought interesting to prepare a chemical derivative of 2.3a that gradually hydrolyzes to 2.3a. In this case, a prodrug of a prodrug is to be prepared a strategy that is referred to as ‘cascade prodrugs’ because it requires a multistep process for bioactivation. Most cascade prodrugs reported in literature are esters, carbamates or phosphate derivatives of amines and are not suitable for derivatization of 2.3a.\textsuperscript{4,7} The ketone moiety in 2.3a seems most suitable for synthetic derivatization that can be reversed \textit{in vivo}. A ketone moiety can be masked in a
number of ways, for instance, by preparing enamines, ketals, thioketals or oxime derivatives. Interestingly, literature reports that oxime hydrolyses is known to be a substantial metabolic pathway and it is greatly influenced by the nature of O-substitution on the oxime\textsuperscript{8,10-14}.

Both substituted and unsubstituted oximes are common in many drugs. The steroid oximes norethisterone-3-oxime (4.1a) and norgestimate (4.1b) and a number of cephalosporin antibiotics like cefdinir and ceftizoxime are examples of such oxime drugs.\textsuperscript{8} The new orally active double prodrug Ro 44-3657 (sibrafiban) is an example of an oxime derivative designed to be bioactivated by enzymatic reduction.\textsuperscript{9} In the case of the aforementioned antibiotics, numerous examples exist of differently substituted oxime derivatives. In general, the oxime moieties are an essential part of the drug and are not designed to hydrolyze to the corresponding ketone but to improve their \textit{in vivo} characteristics. Since the molecular structure of 2.3a contains an $\alpha,\beta$-unsaturated ketone, the reported \textit{in vivo} hydrolysis of the oxime norgestimate to O-acetyl norgestrel is especially interesting.\textsuperscript{10-13,15,16}

We prepared a number of oxime derivatives of 2.3a and its racemate 2.3, in order to study the influence of such derivatization on the pharmacodynamics.\textsuperscript{17} Aiming at \textit{in vivo} hydrolysis of the oximes, we investigated a possible structure activity relationship (SAR) for substituted oximes. Therefore, next to the unsubstituted oxime, several alkylated and acylated oxime derivatives were prepared that could serve as double or even triple prodrugs. For the oxime ether series, four unbranched side chains with increasing length were prepared and two bulky ethers. For the oxime ester series, several acids were selected based on increasing bulkiness and different electronic structure. In order to investigate the effect of an ester, unlikely

\begin{center}
\textbf{Scheme 4.2} The \textit{in vivo} hydrolyses is of the oxime moiety in norethisterone-3-oxime (4.1a) and norgestimate (4.1b) to give norethisterone (4.2a) and O-acetyl norgestrel (4.2b).
\end{center}
to hydrolyze, a tosylate ester was prepared. The actual bioactivation process of the oxime derivatives was not investigated but is assumed to proceed through \textit{in vivo} hydrolysis.

The enone \textbf{2.3} displays no binding affinity for the DA D$_1$ and DA D$_2$ receptors, which both are involved in the pharmacological effect. Therefore, two of the oxime derivatives were evaluated \textit{in vitro} for binding affinity and function at the DA D$_1$ and D$_2$ receptor. All oxime derivatives were evaluated \textit{in vivo} in the Ungerstedt model for Parkinson’s disease.$^{18}$

\section*{4.2 CHEMISTRY}

Synthesis of oxime derivatives of racemic \textbf{2.3} using commercially available hydroxylamine or alkoxylamines is outlined in Scheme 4.3. Regardless of the bulkiness of the alkoxy group, reactions took about the same time for completion. Swift non-aqueous work-up and flash column chromatography using silica pre-treated with gaseous ammonia was necessary to prevent extensive hydrolysis of the oxime. Though the starting material was completely converted during the reaction, hydrolysis during work-up and purification resulted in the isolation of the pure products in moderate yields. The compounds described were isolated as hydrochloride salts that were difficult to recrystallize. Upon recrystallization the products tended to decompose, presumably losing the N,N-di-n-propylamine group leaving a double bond conjugated with the $\alpha$,\$beta$-unsaturated system ($M_w = 148$, detected by GC-MS only).$^1$ Hydroxyl-oxime prodrugs (\textbf{4.3}) and \textit{(-)}-\textbf{4.3} proved hygroscopic as hydrochloride salts and were isolated as maleates. Enantiomerically pure \textit{(-)}-\textbf{4.3} was prepared from \textbf{2.3a} and racemic \textbf{4.3} was prepared from \textbf{2.3}. The oximes are represented in the ‘E’ conformation for convenience only. Literature suggests that the E and Z form are in equilibrium \textit{in vivo}, so no detailed investigation to the spatial orientation of the oximes was performed.$^9$,\$^{14}$

The second part of Scheme 4.3 describes the syntheses of two alkoxylimines to complete the oxime ether series. Several methods are described in literature for alkylating oximes. Use of organic bases (NaOEt, KO$^t$Bu) was found to be inadequate since reactions were incomplete and gave rise to the formation of side products. An inorganic irreversible base, like NaH or K$_2$CO$_3$, followed by a non-aqueous work up proved to be most suitable. Alkyl iodides were used for alkylation since good yields were obtained at room temperature. Alkyl bromides were also used but reacted only upon heating causing formation of several side products.
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Scheme 4.3 Synthesis of oxime ether and ester derivatives of 2.3. Reagents and conditions; (a) RONH$_2$·HCl, MeOH, RT; (b) Compounds 4.8 and 4.9: i) NaH, CH$_2$Cl$_2$, RT ii) RI, RT; Compounds 4.10 - 4.13: R'C, Et$_2$O, RT; Compound 4.14: TsCl, Pyridine, RT.

Ester derivatives of 2.3 were synthesized by acylation of oxime (4.3) with various acyl chlorides as depicted in Scheme 4.3. This was accomplished by adding a solution of (4.3) in dry ether, to a dilute solution of freshly distilled acid chloride in dry ether. The desired products precipitated as their hydrochloride salts and were isolated by filtration. Since the oxime esters were also prone to hydrolysis, aqueous work-up was avoided and products were purified by careful recrystallization. For the preparation of (−)-4.10 the reaction was carried out in dichloromethane with K$_2$CO$_3$ as heterogenic base in the presence of acetic anhydride. This procedure gave similar chemical yield and allowed isolation of the product as a non-hygroscopic maleate that was more easily crystallized.

The conditions used for the preparation of carboxylic esters were not successful in the preparation of tosyloxime (4.14). Therefore, the compound was prepared by reaction of tosyl chloride with 4.3 in pyridine. The different chemical and electronic nature of this sulphonic ester allowed aqueous work up without hydrolysis of the product.

4.3 PHARMACOLOGY

4.3.1 Receptor binding and functional assay

The newly synthesized compounds 4.3 and 4.4 and the reference compounds 5-OH-DPAT and 5,6-di-OH-DPAT were tested for in vitro binding affinity and activity and at the DA
D₁ and D₂ receptors. Binding affinity of 4.3 and 4.4 for the DA D₁ and DA D₂ receptors was determined using rat striatum with [³H]SCH23390 or [³H]Spiperone as radioligands, respectively. In vitro activity at the DA D₁ receptor was determined by stimulation of cAMP production in SK-N-MC cells that normally expresses a DA D₁ receptor. In vitro activity at DA D₂ receptors was determined by stimulation of thymidine incorporation into CHO cells transfected with the human DA D₂ receptor.

4.3.2 In vivo pharmacology

All new compounds were tested on in vivo activity in Ungerstedt’s model for Parkinson’s disease upon oral administration. In this model compounds acting as DA agonists induce rotational behavior in rats. The amount of full contralateral rotations is a measure for a compound to alleviate Parkinson’s disease symptoms in the rat. Upon increasing amount of rotations, a compound is considered more efficacious. Rotations were recorded for 12h after oral administration at several doses of the test compounds. This model is described in detail in Chapter 2.

4.4 RESULTS AND DISCUSSION

4.4.1 In vitro pharmacology

From the functional assays of the tested compounds, it can be seen that compound 4.3 and 4.4 have no intrinsic activity for the DA D₁ receptor (Table 4.1). Binding affinity and intrinsic activity for the DA D₂ receptor are significantly reduced relative to 5-hydroxy-2-(N,N-di-n-propylamino)tetralin (5-OH-DPAT) and 5,6-di-OH-DPAT.

4.4.2 Oxime derivatives in the Ungerstedt model

Table 4.2 shows the total cumulative full contralateral rotations for the tested oximes, 2.3 and the typical DA D₂ agonist 5-OH-DPAT. At 0.3 mg kg⁻¹ po, the racemic 4.4, 4.6, enantiomerically pure (−)-4.3, and (−)-4.10 appear to have reasonable activity as compared to 2.3 and 5-OH-DPAT. Due to the large individual differences in responsiveness between rats, the test results of 4.4, 4.6, (−)-4.3, and (−)-4.10 do not significantly differ from most those of most other oximes tested at 0.3 mg kg⁻¹ po. The results for compound 4.6, for instance, were largely
### Table 4.1

*In vitro* receptor binding affinities (Ki values, nM) and functional assays (% intrinsic activity (EC\textsubscript{50}, nM)) of the tested compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Receptor Binding</th>
<th>Functional assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D\textsubscript{1}</td>
<td>D\textsubscript{2}</td>
</tr>
<tr>
<td>5,6-di-OH-DPAT</td>
<td>157\textsuperscript{b}</td>
<td>0.4\textsuperscript{c}</td>
</tr>
<tr>
<td>5-OH-DPAT</td>
<td>2090</td>
<td>6</td>
</tr>
<tr>
<td>2.3</td>
<td>nd</td>
<td>&gt;10.000</td>
</tr>
<tr>
<td>4.3\textsuperscript{c}</td>
<td>nd</td>
<td>2234</td>
</tr>
<tr>
<td>4.4</td>
<td>nd</td>
<td>2295</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Receptor binding: D\textsubscript{1} binding to rat striatum, radioligand used [\textsuperscript{3}H]SCH 23390 (antagonist); D\textsubscript{2} binding to rat striatum, radioligand used [\textsuperscript{3}H]Spiperone (antagonist). \textsuperscript{b}Binding on hD\textsubscript{1}, L cells, Ki (nM), radioligand used [\textsuperscript{3}H]SCH 23390 (antagonist). \textsuperscript{c}Binding on hD\textsubscript{2}L, CHO K1 cells, radioligand used [\textsuperscript{3}H]N-0437 (agonist). \textsuperscript{d} -, not tested. \textsuperscript{e}tested as a maleate salt.

influenced by one rat from the group that rotated over 11 times more than the other three rats from that group. The inverse was observed for compounds 4.3 and (−)-4.3 that, respectively, had one and two rats that hardly responded to treatment at all.

The pharmacological effects of (−)-4.3 and (−)-4.10 at 0.3 mg kg\textsuperscript{-1} *po* were significantly different from baseline, 30 min post-administration (p < 0.05, two-way ANOVA, Newman-Keuls) and showed a similar pharmacological profile (Figure 4.1). Both oximes showed a more gradual onset of action relative to 2.3\textsubscript{a}, and some rats in the groups tested were still behaviorally activated after 12h when the experiment was stopped. Similarity in pharmacological profile may be explained by a rapid hydrolysis of the acetyl ester of (−)-4.10 to (−)-4.3 from whereon it shares that pharmacological profile.\textsuperscript{19} Compared to 2.3\textsubscript{a} dosed at 0.3 mg kg\textsuperscript{-1} *po*, both (−)-4.3 and (−) −4.10 are to be considered weak. In fact, the pharmacological effects these oximes display at 0.3 mg kg\textsuperscript{-1} *po* are comparable to that of 2.3\textsubscript{a}, dosed at 0.03 mg kg\textsuperscript{-1} *po* (Table 4.2). In the test group of 8 rats, response to treatment with 0.3 mg kg\textsuperscript{-1} *po* of (−)-4.3 varied between 8 and 9020 full contralateral rotations. For (−)-4.10 this was between 299 and 3802 full contralateral rotations.
Table 4.2 The effect of the oxime derivatives of 2.3 and 2.3a at two doses po in Ungerstedt’s model of 6-OH-DA lesioned rats

<table>
<thead>
<tr>
<th>Compound</th>
<th>Group</th>
<th>Total full contralateral turns (X ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.3 mg kg⁻¹</td>
</tr>
<tr>
<td>5-OH-DPAT</td>
<td>R = 0.3 mg kg⁻¹ n b</td>
<td>3072±385 (6)</td>
</tr>
<tr>
<td>2.3</td>
<td>5354±748 (8)</td>
<td>8787±1450 (5)</td>
</tr>
<tr>
<td>2.3a</td>
<td>9531±1715 (8)</td>
<td>-</td>
</tr>
<tr>
<td>2.3a (0.03 mg kg⁻¹ po)</td>
<td>2301±1009 (7)</td>
<td>-</td>
</tr>
<tr>
<td>4.3 d</td>
<td>H</td>
<td>483±340 (4)</td>
</tr>
<tr>
<td>(-)-4.3 d</td>
<td>H</td>
<td>2014±1051 (8)</td>
</tr>
<tr>
<td>4.4</td>
<td>Me</td>
<td>1007±363 (6)</td>
</tr>
<tr>
<td>4.5</td>
<td>Et</td>
<td>176±162 (3)</td>
</tr>
<tr>
<td>4.6</td>
<td>Bn</td>
<td>1652±1351 (4)</td>
</tr>
<tr>
<td>4.7</td>
<td>t-Bu</td>
<td>-</td>
</tr>
<tr>
<td>4.8</td>
<td>n-Pr</td>
<td>943±226 (3)</td>
</tr>
<tr>
<td>4.9</td>
<td>n-Bu</td>
<td>-</td>
</tr>
<tr>
<td>4.10</td>
<td>Acetyl</td>
<td>365±113 (6)</td>
</tr>
<tr>
<td>(-)-4.10 d</td>
<td>Acetyl</td>
<td>2007±460 (8)</td>
</tr>
<tr>
<td>4.11</td>
<td>i-Butyryl</td>
<td>152±138 (3)</td>
</tr>
<tr>
<td>4.12</td>
<td>Pivaloyl</td>
<td>187±48 (3)</td>
</tr>
<tr>
<td>4.13</td>
<td>Benzoyl</td>
<td>-</td>
</tr>
<tr>
<td>4.14</td>
<td>Tosyl</td>
<td>NA e</td>
</tr>
</tbody>
</table>

Numbers noted are the cumulative turns in 12h. n, number of rats tested; -, not tested; *tested as a maleate salt. NA, not active at 10 mg kg⁻¹ po.

At 1.0 mg kg⁻¹ po all of the tested oximes produced a pronounced pharmacological effect; again, tosylxome 4.14 was inactive. Totals for 4.3, 4.4, 4.5, 4.6 and 4.8 were not significantly different from that of 5-OH-DPAT and comparable to the results of 2.3. It should be noted, however, that a total cumulative contralateral turns in 12h of around 9000 to 10000 is considered the maximum physically possible in this model.²⁰
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Figure 4.1 Pharmacological effect of 0.3 mg kg\(^{-1}\) of \((-)\)-4.3 and \((-)\)-4.10 po in the Ungerstedt model for Parkinson’s disease expressed as cumulative full contralateral rotations per 15 min over 12h. Each point is the mean ± s.e.m. for 8 animals tested.

The pharmacological profiles of these oxime ethers at 1.0 mg kg\(^{-1}\) po were similar to those described for \((-)\)-4.3 to \((-)\)-4.10 at 0.3 mg kg\(^{-1}\) po. For the oximes 4.3, 4.4, 4.5 and 4.8, rats were still behaviorally activated after 12h when the experiment was stopped. Oximes 4.5 and 4.13 produced a significant behavioral effect up to 9h after administration. Oximes with the most bulky substituents (4.7, 4.9 and 4.13) show a decreased cumulative pharmacological effect relative to the other oximes. The inactivity of 4.14 \textit{in vivo} is probably due to the distinctly different chemical nature of a tosyl oxime relative to the carboxylic ester and ether derivatives. As mentioned before, most oximes proved to be sensitive to hydrolysis during work-up after synthesis except for 4.14. Reduced absorption of the compound may also contribute to the observed inactivity.

Though only rats entered testing after a good responsiveness to apomorphine had been established (>100 turns h\(^{-1}\) after 50 \(\mu\)g kg\(^{-1}\) sc) some rats failed to respond where others were highly responsive. Differences in responsiveness between rats cause the large variations (SEM)
in the data. Rats with a low response to one oxime prodrug were also found to respond weakly to another. For rats with a high responsiveness to one oxime prodrug, a high response was also observed after administration of other oxime prodrugs.

4.5 CONCLUSIONS

It was shown that all tested oxime derivatives of 2.3 and 2.3a except for 4.14 are able to induce a dopaminergic effect in vivo upon oral administration. The test results of (−)-4.3 and (−)-4.10 from the Ungerstedt rat model indicate that oxime derivatives of 2.3a induce a somewhat slower onset of action and a similar duration of action. At the same dose oxime derivatives of 2.3a appear to be an order of magnitude less potent than 2.3a.

The effects of the oximes (−)-4.3 to (−)-4.10, mentioned in Figure 4.1, dosed at 0.3 mg kg\(^{-1}\) po, are similar to the effect of 2.3a dosed at 0.03 mg kg\(^{-1}\) po. If hydrolysis of the oximes to 2.3a and subsequent bioactivation accounts for the pharmacological effect, then about 10% of these oximes is being bioactivated. At the doses tested we found no clear-cut correlation between the pharmacological effect and the oxime O-substituent.

4.6 EXPERIMENTAL SECTION

4.6.1 Chemistry

General remarks. Melting points were determined in open glass capillaries on an Electrothermal digital melting-point apparatus and are uncorrected. \(^1\)H- and \(^13\)C-NMR spectra were recorded at 200 MHz and 50.3 MHz, respectively, on a Varian Gemini 200 spectrometer. The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Chemical shifts are given in \(\delta\) units (ppm) and are relative to the solvent. Coupling constants are given in Hertz (Hz). The spectra recorded were consistent with the proposed structures. IR spectra were obtained on a ATI-Mattson spectrometer. Electronic ionization (EI) mass spectra were obtained on a Unicam 610-Automass 150 GC-MS system. Chemical ionization (CI) mass spectra were recorded by the Mass Spectrometry Unit of the University of Groningen. Elemental analyses were performed by the Analytical Chemistry Section at Parke Davis (Ann Arbor, MI) or by the Microanalytical Department of the University of Groningen and were within ± 0.4 % of the theoretical values. All chemicals used were commercially
available (Aldrich or Acros) and were used without further purification. Silica (grade 1, 60-120 μm) used for column chromatography was pretreated with gaseous ammonia until saturation.

(±)-6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one oxime ((±)-4.3). Free base of 2.3 (0.48 g, 1.8 mmol) and hydroxylamine hydrochloride (0.19 g, 2.7 mmol) were mixed in methanol (3 mL) and stirred at RT for 18 h. The solvent was removed under reduced pressure and excess aqueous Na₂CO₃ was added that was extracted with ether (3 x 20 mL). The combined ethereal layers were dried (MgSO₄), filtered and evaporated to give 0.51 g of a pale brown oil which could be crystallized from hexane (3 mL). Yield: 0.37 g, 1.4 mmol (78%), mp 103-104°C. The oxime was converted to the maleate salt, mp 163-166°C, IR (free base, KBr) 3287, 2930, 1454; ¹H-NMR (CDCl₃) δ 2.72-2.78 (m, 1H), 2.59 (dd, 1H), 2.47 (br s, 4H), 2.19-2.28 (m, 1H), 2.02-2.15 (m, 5H), 2.03 (d, 1H), 1.91 (m, 1H), 1.72-1.79 (m, 1H), 1.56-1.67 (m, 1H), 1.35-1.49 (m, 5H), 0.89 (t, 6H) ppm. ¹³C-NMR (CDCl₃) δ 155.7, 141.0, 125.5, 61.4, 52.5, 34.1, 24.9, 24.3, 22.8, 20.9, 11.8 ppm; MS (EI) m/z 264 (M⁺); Anal. (C₁₆H₂₈N₂O·C₄H₄O₄) C, H and N.

(−)-6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one oxime, (−)-4.3a. Free base of 2.3a (0.48 g, 1.8 mmol) and hydroxylamine hydrochloride (0.19 g, 2.7 mmol) were mixed in methanol (3 mL) and stirred at RT for 18 h. The solvent was removed under vacuum and excess aqueous Na₂CO₃ was added which was extracted with ether (3 x 20 mL). The combined ethereal layers were dried (MgSO₄), filtered and evaporated to give 0.55 g of a pale brown oil which could be crystallized from hexane (3 mL). Yield: 0.35 g, 1.3 mmol (74%), mp 100-102°C. The oxime then was converted to the maleate salt, mp 165-167°C, [α]₂₀D = −93.6° (c = 0.28, methanol), IR (free base, KBr) 3287, 2930, 1454; ¹H-NMR (CDCl₃) δ 2.72-2.78 (m, 1H), 2.59 (dd, 1H), 2.47 (br s, 4H), 2.19-2.28 (m, 1H), 2.02-2.15 (m, 5H), 2.03 (d, 1H), 1.91 (m, 1H), 1.72-1.79 (m, 1H), 1.56-1.67 (m, 1H), 1.35-1.49 (m, 5H), 0.89 (t, 6H) ppm. ¹³C-NMR (CDCl₃) δ 155.7, 141.0, 125.5, 61.4, 52.5, 34.1, 24.9, 24.3, 22.8, 20.9, 11.8 ppm; MS (EI) m/z 264 (M⁺); Anal. (C₁₆H₂₈N₂O·C₄H₄O₄) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-methyl-oxime (4.4). The procedure for 4.3 was followed but using O-methyl-hydroxylamine hydrochloride. After work up the resulting colorless oil was converted to hydrochloride salt.
Yield: 0.41 g, 1.5 mmol (80%), mp 197-198°C; IR (KBr) 2963, 2600, 2448, 1437, 1053 cm\(^{-1}\); \(^1\)H-NMR 500MHz (CDCl\(_3\)) \(\delta\) 3.86 (s, 3H), 2.71-2.77 (m, 1H), 2.60 (dd, 1H), 2.48 (br s, 4H), 2.23-2.30 (m, 1H), 2.03-2.16 (m, 5H), 2.03 (d, 1H), 1.93 (m, 1H), 1.71-1.78 (m, 1H), 1.57-1.66 (m, 1H), 1.37-1.51 (m, 5H), 0.88 (t, 6H) ppm. \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 155.7, 141.0, 125.5, 61.4, 56.5, 52.5, 34.1, 24.9, 24.3, 22.8, 20.9, 11.8 ppm; MS (EI) \(m/z\) 264 (M\(^+\)); Anal. (C\(_{17}\)H\(_{30}\)N\(_2\)O·HCl) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2\(^H\)-naphthalen-1-one \(O\)-ethyl-oxime (4.5). The procedure for 4.3 was followed but using \(O\)-ethyl-hydroxylamine hydrochloride. After work up the resulting colorless oil was purified by flash chromatography (silica, dichloromethane/ethanol, 20:1) and was converted to hydrochloride salt. Yield: 0.42 g, 1.3 mmol (71%), mp 120-123°C. IR (KBr) 2965, 2601, 2513, 1475, 1053 cm\(^{-1}\); \(^1\)H-NMR (HCl-salt, CD\(_3\)OD) \(\delta\) 4.06 (q, 2H), 3.67 (s, 1H), 3.11-3.32 (m, 4H), 2.80 (s, 1H), 2.72 (s, 1H), 2.48 (s, 1H), 2.14-2.23 (m, 6H), 1.78 (br s, 7H), 1.22 (t, 3H), 1.03 (t, 6H) ppm; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 154.1, 136.6, 125.6, 68.6, 59.6, 52.1, 30.7, 30.3, 22.7, 22.6, 22.2, 20.3, 18.2, 17.9, 13.3, 9.7 ppm; MS (El) \(m/z\) 292 (M\(^+\)); Anal. (C\(_{18}\)H\(_{33}\)N\(_2\)O·1.75HCl) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2\(^H\)-naphthalen-1-one \(O\)-benzyl-oxime (4.6). The procedure for 4.3 was followed but using \(O\)-benzyl-hydroxylamine hydrochloride. After work up the resulting colorless oil was purified by flash chromatography (silica, dichloromethane/ethanol, 20:1) and was converted to hydrochloride salt. Yield: 0.45 g, 1.2 mmol (65%), mp 120-122 °C. IR (KBr) 2960, 2660, 2446, 1009 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 7.26-7.40 (m, 5H), 2.74-2.88 (m, 2H), 2.23-2.57 (m, 7H), 1.88-2.17 (m, 6H), 1.34-1.74 (m, 8H), 0.87 (t, 6H) ppm; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 156.1, 141.0, 138.5, 128.1, 128.0, 127.4, 125.6, 75.4, 56.2, 52.4, 34.1, 30.5, 24.8, 24.2, 23.0, 21.7, 20.7, 11.7 ppm; MS (El) \(m/z\) 354 (M\(^+\)); Anal. (C\(_{23}\)H\(_{34}\)N\(_2\)O-HCl) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2\(^H\)-naphthalen-1-one \(O\)-t-butyl-oxime (4.7). The procedure for 4.3 was followed but using \(O\)-t-butyl-hydroxylamine hydrochloride. After work up the resulting colorless oil was purified by flash chromatography (silica, dichloromethane/ethanol, 20:1) and was converted to hydrochloride salt. Yield: 0.43 g, 1.2 mmol (67%), mp 152-157°C. IR (KBr) 2971, 2398, 1190, 951 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\)
1.99-2.80 (m, 13H), 1.32-1.73 (m, 8H), 1.27 (s, 9H), 0.87 (t, 6H) ppm; $^{13}$C-NMR (CDCl$_3$) δ 152.7, 139.0, 126.7, 56.2, 52.4, 34.0, 30.5, 27.3, 24.9, 24.3, 22.7, 21.8, 20.9, 11.7 ppm; MS (EI) m/z 320 (M$^+$); Anal. (C$_{20}$H$_{34}$N$_2$O-HCl) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-(n-propyl)-oxime (4.8). Oxime 4.3 (0.50 g, 1.9 mmol) was dissolved in dichloromethane (10 mL). NaH (60% dispersion in mineral oil; 0.080 g, 2.0 mmol) was added in small portions. After stirring at RT for 15 min, n-propyl iodide (0.25 mL, 2.6 mmol) was introduced and stirring was continued overnight. Work up by addition of ether (50 mL) and filtration. The solvent was evaporated and the resulting oil purified by flash chromatography (silica, dichloromethane/ethanol, 20:1) and subsequently converted to hydrochloride salt. Yield: 0.37 g, 1.1 mmol (58%), mp 134-135°C. IR (KBr) 2963, 2435, 1458, 982 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ 4.00 (t, 3H), 2.70-2.84 (m, 2H), 2.56-2.66 (m, 2H), 2.40-2.48 (m, 4H), 2.00-2.36 (m, 7H), 1.58-1.95 (m, 5H), 1.33-1.55 (m, 5H), 0.92 (t, 3H), 0.87 (t, 3H) ppm; $^{13}$C-NMR (CDCl$_3$) δ 155.5, 140.5, 125.7, 75.1, 56.2, 34.0, 24.8, 24.2, 22.8, 21.7, 20.8, 11.7 ppm; MS (EI) m/z 306 (M$^+$); Anal. (C$_{19}$H$_{34}$N$_2$O-HCl) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-(n-butyl)-oxime (4.9). Oxime 4.3 (0.50 g, 1.9 mmol) was dissolved in dichloromethane (10 mL). NaH (60% dispersion in mineral oil; 0.080 g, 2.0 mmol) was added in small portions. After stirring at RT for 15 min, n-butyl iodide (0.32 mL, 2.6 mmol) was introduced and stirring was continued overnight. Work up by addition of ether (50 mL) and filtration. The solvent was evaporated and the resulting oil purified by flash chromatography (silica, dichloromethane/ethanol, 20:1) and subsequently converted to hydrochloric salt. A small portion of the free base was precipitated with (–)-ditoluyltartaric acid. Recrystallization from iso-propyl acetate gave a white powder that was used for microanalysis. Yield: 0.43 g, 1.2 mmol (63%), mp 102-105°C. IR (KBr) 2956, 2543, 1470, 1028 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) δ 4.00 (t, 3H), 2.70-2.84 (m, 2H), 2.56-2.66 (m, 2H), 2.40-2.48 (m, 4H), 2.00-2.36 (m, 7H), 1.58-1.95 (m, 5H), 1.33-1.55 (m, 5H), 0.92 (t, 3H), 0.87 (t, 3H) ppm; $^{13}$C-NMR (CDCl$_3$) δ 155.5, 140.5, 125.7, 75.1, 56.2, 34.0, 24.8, 24.2, 22.8, 21.7, 20.8, 11.7 ppm; MS (EI) m/z 320 (M$^+$); Anal. (C$_{20}$H$_{36}$N$_2$O-HCl) C, H and N.
6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-acetyl-oxime (4.10). Oxime 4.3 (0.20 g, 0.76 mmol) was dissolved in dry ether (10 mL). A solution of freshly distilled acetylchloride (0.059 g, 0.75 mmol) in dry ether (10 mL) was added dropwise at RT. After stirring for 3 h the hydrochloride precipitate was filtered and thoroughly washed with hot ether. Yield: 0.22 g, 0.49 mmol (64%), mp 138-140°C. IR (KBr) 2967, 2448, 1764, 1221, 1005 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.62-2.92 (m, 3H), 2.39-2.47 (m, 4H), 2.04-2.20 (m, 8H), 1.60-1.98 (m, 4H), 1.34-1.51 (m, 5H), 0.87 (t, 3H) ppm; ¹³C-NMR (CDCl₃) δ 178.9, 162.6, 146.7, 125.2, 55.9, 34.6, 30.5, 24.4, 24.2, 24.0, 21.7, 20.5, 19.6, 11.6 ppm; MS (EI) m/z 306 (M⁺); Anal. (C₁₈H₃₀N₂O₂·1.3HCl) C, H and N.

(--)-6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-acetyl-oxime ((--)-4.10). Optical pure (--)-PD166804 (0.30 g free base, 1.14 mmol) and K₂CO₃ (2.0 g, 14 mmol) were mixed in dichloromethane (30 mL). At 0°C and vigorous stirring a solution of acetic anhydride (0.15 mL, 1.35 mmol) in dichloromethane (20 mL) was added dropwise. After 30 min, stirring at 0°C the temperature was allowed to rise to RT and stirring was continued overnight. Methanol (20 mL) was added to consume excess anhydride and after 10 min stirring the mixture was filtered through Celite (1 g). The residue was washed with ethyl acetate and the filtrate was evaporated. The crude product was subsequently stripped with ethyl acetate (3 x 20 mL) and isopropyl acetate (20 mL) and converted to the maleate. Recrystallization from isopropyl acetate gave pure (--)-4.10. Yield: 0.32 g, 0.76 mmol (67%); mp 180-182°C; [α] = -113° (c = 0.23, methanol); Anal. (C₁₈H₃₀N₂O₂·C₄H₄O₄) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-i-butyryl-oxime (4.11). The procedure for 4.10 was followed but using iso-butyryl chloride. Yield: 0.11 g, 0.28 mmol (38%), mp 98-101°C. IR (KBr) 2965, 2410, 1760, 1099 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.66-2.87 (m, 4H), 2.40-2.48 (m, 4H), 2.10-2.39 (m, 5H), 1.90 (d, 2H), 1.60-180 (m, 2H), 1.40-1.51 (m, 5H), 1.22 (d, 6H), 0.86 (t, 6H) ppm; ¹³C-NMR (CDCl₃) δ 173.0, 161.6, 144.9, 124.0, 54.8, 51.0, 33.3, 31.7, 29.2, 23.0, 22.9, 22.7, 20.2, 19.2, 17.6, 10.3 ppm; MS (EI) m/z 334 (M⁺); Anal. (C₁₉H₃₂N₂O₂·HCl) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-pivaloyl-oxime (4.12). The procedure for 4.10 was followed but using pivaloyl chloride. Yield: 0.26 g, 0.66 mmol (87%), mp 109-111°C. IR (KBr) 2968, 2421, 1753, 1111 cm⁻¹; ¹H-NMR (CDCl₃) δ
6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-benzoyloxime (4.13). The procedure for 4.10 was followed but using benzyol chloride. Yield: 0.30 g, 0.74 mmol (98%), mp 156-159°C. IR (KBr) 2966, 2045, 1744, 1257, 1086 cm⁻¹; ¹H-NMR (CDCl₃) δ 8.05 (d, 2H), 7.35-7.50 (m, 3H), 2.92-3.03 (m, 2H), 2.80 (s, 1H), 2.61-2.68 (m, 5H), 2.36-2.59 (m, 3H), 2.01-2.14 (m, 3H), 1.78-1.83 (m, 2H), 1.53-1.67 (m, 5H), 0.91 (t, 6H) ppm; ¹³C-NMR (CDCl₃) δ 162.5, 161.9, 144.4, 131.6, 129.0, 128.0, 127.0, 126.2, 124.0, 55.3, 50.6, 32.8, 29.2, 23.0, 22.7, 22.5, 19.2, 18.9, 10.3; MS (EI) m/z 368 (M⁺); Anal. (C₂₃H₃₂N₂O₂·1.1HCl) C, H and N.

6-(N,N-di-n-Propylamino)-3,4,5,6,7,8-hexahydro-2H-naphthalen-1-one O-tosyl-oxime (4.14). Oxime 4.3 (5.0 g, 19 mmol) was dissolved in pyridine (25 mL). At 0°C, tosyl chloride (10.9 g, 57 mmol) was added slowly. After stirring for 1 h the temperature was allowed to rise to RT and the mixture was stirred overnight. The reaction mixture is then poured on ice water and subsequently extracted with dichloromethane (10 x 50 mL). The combined extracts were dried (Na₂SO₄) and evaporated to give 8.4 g of a dark oil. This was stripped with toluene (3 x 50 mL) to give a brown solid, which was dissolved in dry ether (150 mL). Addition of 1N ethereal HCl and filtration gave the product as a hydrochloride salt. Recrystallization from isopropanol/ether gave 5.6 g, 13 mmol (68%), mp 158 °C (dec.). IR (KBr) 2961, 2410, 1370, 1190, 813 cm⁻¹; ¹H-NMR (HCl-salt, CD₃OD) δ 7.80 (d, 2H), 7.41 (d, 2H), 3.56 (m, 1H), 3.05-3.25 (m, 4H), 2.81 (dt, 1H), 2.30-2.53 (m, 7H), 2.17 (br s, 4H), 1.67-1.86 (m, 7H), 1.01 (t, 3H) ppm; ¹³C-NMR (CDCl₃) δ 162.3, 145.0, 144.2, 132.5, 129.2, 128.4, 122.8, 58.9, 52.1, 30.8, 29.4, 23.0, 22.2, 20.0, 19.7, 18.1, 17.8, 9.6 ppm; MS (Cl) m/z 419 (M+1); Anal. (C₂₃H₃₄N₂SO₃·HCl) C, H, N and Cl.
4.6.2 Pharmacology.

All compounds were tested as hydrochloride salts unless noted otherwise. All in vitro and in vivo experiments were performed at Parke Davis Pharmaceutical Research Division (Ann Arbor, MI. USA).

Receptor binding studies and functional assays. The methods for determining the affinity of the compounds for brain DA D₁ and D₂ receptors using [³H]SCH-23390 or [³H]Spiperone respectively are described in chapter 2, as are the methods for determining the intrinsic activity of the compounds at the DA D₁ and D₂ receptor.

The Ungerstedt model for Parkinson’s disease rats.¹⁸ Contralateral turning experiments were essentially according to the original reference by Ungerstedt and Arbuthnott. Briefly, rats were lesioned in right medial forebrain bundle (P4.8 mm, L1.1 mm, V-8.2 mm from bregma) with 8 mg 4 mL⁻¹ of 6-hydroxy-dopamine HBr in saline with ascorbic acid 1 mg ml⁻¹ added. After 3 weeks recovery, completeness of lesion was assessed with apomorphine 50 mg kg⁻¹ sc. Only animals rotating more than 100 turns in an hour were used in subsequent experiments. Rats were removed from home cages in morning, weighed, dosed and placed into harnesses in rotator apparatus. Rats sit in stainless steel, flat bottomed, hemispheric bowls and are connected via the harness and a flexible spring tether to an automated data collection system. Data is presented as full rotations in contralateral directions. Rats are used once weekly.

4.7 REFERENCES


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