Orally Active Oxime Derivatives of the Dopaminergic Prodrug 6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one. Synthesis and Pharmacological Activity

Bastiaan J. Venhuis,† Durk Dijkstra,† David Wustrow,‡ Len T. Meltzer,‡ Lawrence D. Wise,‡ Stephen J. Johnson,‡ and Håkan V. Wikström*,†

Department of Medicinal Chemistry, University Center for Pharmacy, University of Groningen, Antonius Deusinglaan 1, NL-9713 AV Groningen, The Netherlands, and Department of Chemistry and CNS Pharmacology, Pfizer Global Research & Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, Michigan 48105

Received January 15, 2003

A series of racemic and enantiomerically pure oxime derivatives of the potential anti-Parkinson prodrug 6-(*N,N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (**1**) were synthesized and pharmacologically evaluated. The oximes induced rotational behavior in the Ungerstedt rat rotation model for Parkinson's disease after oral administration. Especially the unsubstituted oxime ((−)-**3**) and the acetyl-oxime ((−)-**10**) induced a pronounced and long lasting effect. In this model, large individual differences were observed in responsiveness to treatment between rats. Though less potent than the parent prodrug, the oxime derivatives of (±)-**1** and (−)-**1** can be orally active, acting as cascade prodrugs.

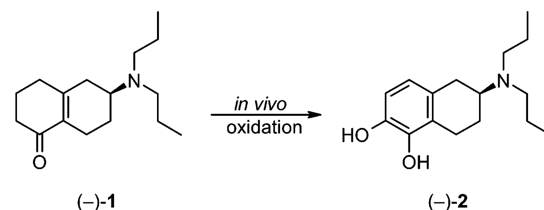
Introduction

The synthesis and pharmacological evaluation of the orally active enone prodrug *S*-(−)-6-(*N,N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one ((−)-**1**), and several of its analogues have been reported previously (Scheme 1).[1−4] Bioactivation of enones by metabolic conversion to their corresponding catecholamines, as was demonstrated for (−)-**1**, is thought to be the general bioactivation mechanism. Catecholamines such as (−)-5,6-dihydroxy-2-(*N,N*-di-*n*-propylamino)tetralin ((−)-5,6-diOH-DPAT, (−)-**2**) are known mixed dopamine (DA) D_1/D_2 agonists with potential utility in the treatment of Parkinson's disease.[5−10] Prodrugs of such catecholamines may increase their usefulness by improving the bioavailability or extending the duration of action.

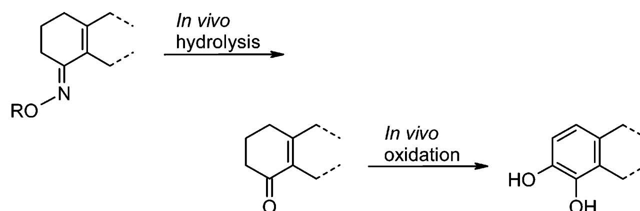
To potentially further increase the usefulness of these enone prodrugs the possibility of preparing 'cascade prodrugs' of **1** was investigated. Since enones are easily converted to oximes and oxime hydrolysis is described to be a substantial metabolic pathway, greatly influenced by the nature of substitution on the oxime oxygen atom, a number of oxime ethers and oxime esters of (−)-**1** and (±)-**1** were prepared (Scheme 2).[11−15]

For the oxime ether series, four unbranched alkyl groups with increasing length were selected and two bulky side chains. For the oxime ester series, several acids were selected based on increasing bulkiness and different electronic structure. To investigate the effect of a different type of ester, a tosylate ester was prepared. Aiming at in vivo hydrolysis of the oximes, we investigated a possible structure−activity relationship (SAR) for these potential 'cascade prodrugs' in the Ungerstedt rat rotation model for Parkinson's disease.[16]

Scheme 1. Bioactivation of (−)-**1** to the Mixed DA D_1/D_2 Agonist (−)-**2**



Scheme 2. An Oxime Acting as a 'Cascade' Prodrug of a Catecholamine



Although (±)-**1** displays no binding affinity for the DA D_1 and DA D_2 receptors, the binding affinity and functional effects of two oximes were evaluated at these receptors.[1,17]

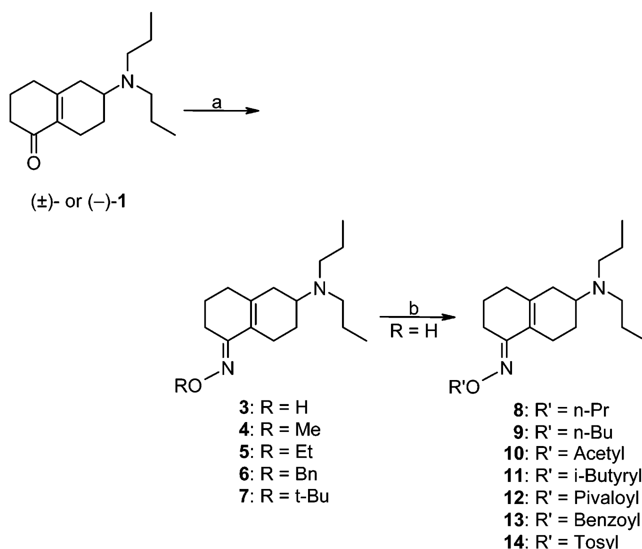
Chemistry

The synthesis of the oxime derivatives is outlined in Scheme 3. Enone (±)-**1** or (−)-**1** was treated with 1.5 equiv of (*O*-alkyl)-hydroxylamine at room temperature (RT) until all starting material was consumed. Moderate yields were obtained due to the hydrolysis of the oxime during its isolation and loss of the *N,N*-di-*n*-propylamine group upon recrystallization as a hydrochloride salt.[1] The hydrochloride salts of oximes (±)-**3** and (−)-**3** proved hygroscopic and were therefore isolated as maleates. Alkylation of (±)-**3** using NaH and an alkyl iodide gave two more alkoxylimines to complete the oxime ether series. Since Okamoto et al. and Weller et al. have

* Corresponding author. Tel: +31-50-3633310, Fax: +31-50-3636908, E-mail: H.V.Wikström@farm.rug.nl.
† University of Groningen.
‡ Pfizer Global Research & Development.

10.1021/jm0307786 CCC: $25.00 © 2003 American Chemical Society
Published on Web 08/19/2003

Scheme 3[a]



[a] Reagents and conditions: (a) $RONH_2{\cdot}HCl$, MeOH, RT; (b) Compounds **8** and **9**: (i) NaH, CH_2Cl_2, RT, (ii) RI, RT; compounds **10**−**13**: R′Cl, Et_2O, RT; compound **14**: TsCl, pyridine, RT.

reported that the *E* and *Z* conformation of oximes are in equilibrium in vivo, the oximes are represented in the '*E* conformation for convenience only.[13,18]

Ester derivatives of (±)-**3** were prepared by acylation with various acyl chlorides as depicted in Scheme 3. This was accomplished by adding a solution of (±)- or (−)-**3** in dry ether, to a dilute solution of freshly distilled acid chloride in dry ether. The desired products were isolated by filtration and subsequently recrystallized carefully. The preparation of (−)-**10** was carried out in dichloromethane with K_2CO_3, in the presence of acetic anhydride. This procedure gave similar chemical yield and allowed isolation of the product as a nonhygroscopic maleate salt that was more easily crystallized. The conditions used for the preparation of carboxylic esters were not successful in the preparation of tosylate (±)-**14**. Therefore, the compound was prepared by reaction of tosyl chloride with (±)-**3** in pyridine.

Hydrolysis of the oximes was observed by TLC analysis under acidic (pH = 3) and alkaline (pH = 9) conditions that initially were used in the workup procedures. Within several minutes, all but one oxime had partially converted back to **1** thereby noticeably reducing the chemical yield. Remarkably, only the sulfonic acid ester (±)-**14** was stable under aqueous conditions. Since aqueous workup especially limited the chemical yield of compounds (±)-**8** to (±)-**13**, nonaqueous workup conditions were preferred.

Pharmacology

Compounds (±)-**3** and (±)-**4** and some reference compounds were tested for in vitro binding affinity and activity at the DA D_1 and D_2 receptors. All new oximes were tested in vivo in the Ungerstedt rat rotation model, which is an accepted model for studying DA agonist efficacy and their potential utility in the treatment of Parkinson's disease.[16] In this model, rats receive a unilateral lesion of the medial forebrain bundle that projects dopaminergic neurons to the striatum. This lesion results in DA receptors becoming supersensitive in the striatum on the lesioned side. Administration of a centrally acting DA agonist causes disproportionate stimulation of locomotor activity, making the rats circle contralaterally to the lesioned side of the brain. The more rotations per unit time, the more efficient a compound is considered to be for treating parkinsonian symptoms. Rotations were recorded for 12 h after oral administration at several doses of the oximes tested.

To investigate whether stimulation of DA D_1 and DA D_2 receptors contributed to the observed rotational behavior, a blocking study was carried out using selective DA D_1 and DA D_2 antagonists.

Table 1. In Vitro Receptor Binding Affinities (K_i values, nM) and Functional Assays (% intrinsic activity (EC_{50}, nM)) of the Oximes and Reference Compounds[a]

compound	receptor binding D_1	receptor binding D_2	functional assay D_1	functional assay D_2
(±)-**1**	nd[b]	>10000	0%	nd
(±)-**2**	170	3	80% (nd)	100% (0.7)
(±)-**3**	nd	2234	0%	77% (170)
(±)-**4**	nd	2295	0%	22% (>1000)

[a] Receptor binding to rat striatum (n = 3, SEM < 10%); D_1 ([^{3}H]SCH23390), D_2 ([^{3}H]spiperone). Functional assay: D_1 activity by stimulation of cAMP production in SK-N-MC cells. D_2 activity by stimulation of thymidine incorporation into CHO cells transfected with the hD_2 receptor. [b] nd, not determined.

Table 2. Effect of the of Oxime Derivatives of (±)-**1** and (−)-**1** at Two Doses po in Ungerstedt's Model of 6-OH-DA Lesioned Rats[a]

compd	R of RO−N= group	total full contralateral turns (X ± SEM) 0.3 mg kg^{-1}	n[b]	1.0 mg kg^{-1}	n
(±)-**1**		5354 ± 748	(8)	8787 ± 1450	(5)
(−)-**1**		9531 ± 1715	(8)	-	-
(−)-**1** (0.03 mg kg^{-1} po)		2301 ± 1009	(7)	-	-
3[d]	H	483 ± 340	(4)	6048 ± 1152	(5)
(−)-**3**[d]	H	2014 ± 1051	(8)	-	-
4	Me	1007 ± 363	(6)	5295 ± 1379	(6)
5	Et	176 ± 162	(3)	4217 ± 903	(6)
6	Bn	1652 ± 1351	(4)	4702 ± 1814	(4)
7	t-Bu	-	-	2118 ± 501	(6)
8	n-Pr	943 ± 226	(3)	5406 ± 1016	(6)
9	n-Bu	-	-	1364 ± 508	(4)
10	acetyl	365 ± 113	(6)	-	-
(−)-**10**	acetyl	2007 ± 460	(8)	-	-
11	*i*-butyryl	152 ± 138	(3)	-	-
12	pivaloyl	187 ± 48	(3)	-	-
13	benzoyl	-	-	2280 ± 734	(3)
14[d]	tosyl	NA	(3)	NA	(3)

[a] Numbers noted are the cumulative turns in 12 h. [b] n, number of rats tested. [c] -, not tested. [d] NA, not active at 10 mg kg^{-1} po.

Results and Discussion

Receptor Binding and Functional Assay. From Table 1 it is evident, that like reference compound (±)-**1**, both (±)-**3** and (±)-**4** are inactive at the DA D_1 and DA D_2 receptor. In contrast to that, the active metabolite ((±)-**2**)) displays a high binding affinity for both receptor subtypes.

The Ungerstedt Rat Model for Parkinson's Disease. Table 2 shows the total cumulative full contralateral rotations for the tested oximes and the parent enone (±)-**1**. Both at 0.3 mg kg^{-1} po and at 1.0 mg kg^{-1} po all the oximes tested except (±)-**14** were able to induce rotational behavior. At 0.3 mg kg^{-1} po, the pharmacological effects of (±)-**4**, (±)-**6**, (−)-**3**, and (−)-**10** were significantly different from baseline 30 min after administration ($p < 0.05$, two-way ANOVA, New-

man-Keuls) and the onset of action was more gradual then was observed for (±)-**1**. When the experiment was stopped after 12 h, rats were still behaviorally activated. The pharmacological effects of both (−)-**3** and (−)-**10** at 0.3 mg kg^{-1} po are comparable to that of (−)-**1**, dosed at 0.03 mg kg^{-1} po (Table 2).

At 1.0 mg kg^{-1} po, oximes (±)-**3**, (±)-**4**, (±)-**6**, and (±)-**8** induced pharmacological effects until the experiment was stopped after 12 h. Oximes (±)-**5**, (±)-**7**, (±)-**9**, and (±)-**13** induced significant pharmacological effects ranging from 6 to 9 h after administration. At this dose, the onset of action was similar to that observed for (±)-**1**. Compound (±)-**14** was found inactive up to 10 mg kg^{-1} po.

Some rats failed to respond to treatment with oximes while others were highly responsive, even though rats only entered testing after a good responsiveness to apomorphine had been established (>100 turns h^{-1} after 50 μg kg^{-1} sc). Rats were consistent in their high or low responsiveness when treated with different oximes. Differences in the bioactivation enzymatic activity between the oximes may be contributing to this consistency.

Rotational behavior induced by (±)-**5** (1.0 mg kg^{-1} po) was reduced by 25 ± 9% when pretreated with haloperidol (D_2 antagonist, 0.3 mg kg^{-1} ip) and by 10 ± 4% when pretreated with SCH23390 (D_1 antagonist, 0.03 mg kg^{-1} ip)(n = 4). After pretreatment with both antagonists rotational behavior was reduced by 75 ± 12% (n = 4). This clearly demonstrates the involvement of DA D_1 and DA D_2 receptor subtypes in inducing the observed rotational behavior.

In conclusion, in agreement with literature it was shown that also the oxime derivatives of (±)-**1** or (−)-**1** readily hydrolyze under acidic and alkaline conditions. Since these oximes as well as (±)-**1** are inactive at the DA receptor, yet induce DA D_1 and DA D_2 receptor related effects in vivo, it is likely that the oximes described act as cascade prodrugs. An enone moiety can therefore be successfully be masked by derivatization to an oxime. The only inactive compound in the series was (±)-**14** that also was the only oxime stable under aqueous conditions. Mainly because of large individual differences in the in vivo model, no clear-cut SAR could be identified.

Though the pharmacological effect of the tested oximes was not as strong as that of (±)-**1** or (−)-**1**, we have shown that oximes can be orally active and are efficacious in the Ungerstedt rat rotation model of Parkinson's disease up to 12 h after administration.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries on an Electrothermal digital melting-point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200 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 δ units (ppm) and are relative to the solvent. 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 Pfizer (Ann Arbor, MI) or by the Microanalytical Department of the University of Groningen and were within ±0.4% of the theoretical values, except where noted. 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-2*H*-naphthalen-1-one Oxime ((±)-3). Free base of (±)-**1** (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 Na_2CO_3 was added which was extracted with ether (3 × 20 mL). The combined ethereal layers were dried ($MgSO_4$), 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 then was converted to the maleate salt, mp 163−166 °C, IR (free base, KBr) 3287, 2930, 1454; ^1H NMR ($CDCl_3$) 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. ^{13}C NMR ($CDCl_3$) 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. ($C_{16}H_{28}N_2O$) C, H, N.

(−)-6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one Oxime ((−)-3). Free base of (−)-**1** (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 Na_2CO_3 was added which was extracted with ether (3 × 20 mL). The combined ethereal layers were dried ($MgSO_4$), 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, $[\alpha]^{20}_D = -93.6°$ (c = 0.28, methanol), IR (free base, KBr) 3287, 2930, 1454; ^1H NMR ($CDCl_3$) 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. ^{13}C NMR ($CDCl_3$) 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. ($C_{16}H_{28}N_2O \cdot C_4H_4O_4$) C, H, N.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O*-Methyloxime (4). The procedure for **3** was followed but using *O*-methylhydroxylamine hydrochloride. After workup, 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}; ^1H NMR 500 MHz ($CDCl_3$) δ 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 ($CDCl_3$) δ 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 278 (M^+); Anal. ($C_{17}H_{30}N_2O \cdot HCl$) C, H, N.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O*-Ethyloxime (5). The procedure for **3** was followed but using *O*-ethylhydroxylamine hydrochloride. After workup, 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}; ^1H NMR (HCl salt, CD_3OD) δ 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 ($CDCl_3$) δ 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 (EI) m/z 292 (M^+); Anal. ($C_{18}H_{33}N_2O \cdot 1.75HCl$) C, H, N, Cl.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O*-Benzyloxime (6). The procedure for **3** was followed but using *O*-benzylhydroxylamine hydrochlo-

ride. After workup, 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$_3$) δ 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$_3$) δ 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 (EI) *m/z* 354 (M$^+$); Anal. ($C_{23}H_{34}N_2O$·HCl) C, H, N.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O-tert*-Butyloxime (7). The procedure for **3** was followed but using *O-tert*-butyl-hydroxylamine hydrochloride. After workup, 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$_3$) δ 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. ($C_{20}H_{36}N_2O$·HCl) C, H, N.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O-n*-Propyloxime (8). Oxime **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. Workup 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. ($C_{19}H_{34}N_2O$·HCl).

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O-n*-Butyloxime (9). Oxime **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*-butyliodide (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. 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. ($C_{20}H_{36}N_2O$· HCl) C, H, N.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O*-Acetyloxime (10). Oxime **3** (0.20 g, 0.76 mmol) was dissolved in dry ether (10 mL). A solution of freshly distilled acetyl chloride (0.059 g, 0.75 mmol) in dry ether (10 mL) was added dropwise at RT. After being 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}; ^{1}H NMR (CDCl$_3$) 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; ^{13}C NMR (CDCl$_3$) 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. ($C_{18}H_{30}N_2O_2$·1.3HCl) C, H, N, Cl.

(−)-6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O*-Acetyloxime ((−)-10). (−)-**3** (0.30 g free base, 1.14 mmol) and K_2CO_3 (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 of 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 of 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 × 20 mL) and isopropyl acetate (20 mL) and converted to the maleate. Recrystallization from isopropyl acetate gave pure (−)-**10**. Yield: 0.32 g, 0.76 mmol (67%); mp 180−182 °C; [α] = −113° (*c* = 0.23, methanol); Anal. ($C_{18}H_{30}N_2O_2$·$C_4H_4O_4$) C, H, N.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O-i*-Butyryloxime (11). Preparation according to the method used for **10**, using isobutyryl chloride. Yield: 0.11 g, 0.28 mmol (38%), mp 98−101 °C. IR (KBr) 2965, 2410, 1760, 1099 cm^{-1}; ^{1}H NMR (CDCl$_3$) 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; ^{13}C NMR (CDCl$_3$) 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. ($C_{20}H_{34}N_2O_2$·HCl) C, H, N.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O*-Pivaloyloxime (12). Preparation according to the method used for **10**, using pivaloyl chloride. Yield: 0.26 g, 0.66 mmol (87%), mp 109−111 °C. IR (KBr) 2968, 2421, 1753, 1111 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.81 (dt, 2H), 2.75 (s, 1H), 2.39−2.49 (m, 5H), 2.13−2.33 (m, 4H), 2.10 (d, 2H), 1.73−1.79 (m, 2H), 1.371.52 (m, 5H), 1.27 (s, 9H), 0.87 (t, 6H) ppm; ^{13}C NMR (CDCl$_3$) δ 173.8, 161.8, 144.9, 124.0, 54.8, 51.0, 33.3, 31.7, 29.2, 25.8, 23.0, 22.9, 22.7, 20.2, 19.2, 10.3 ppm; MS (EI) *m/z* 348 (M$^+$); Anal. ($C_{21}H_{36}N_2O_2$·1.2HCl) C, H, N, Cl.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O*-Benzoyloxime (13). Preparation according to the method used for **10**, using benzoyl chloride. Yield: 0.30 g, 0.74 mmol (98%), mp 156−159 °C. IR (KBr) 2966, 2045, 1744, 1257, 1086 cm^{-1}; ^{1}H NMR (CDCl$_3$) 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; ^{13}C NMR (CDCl$_3$) 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. ($C_{23}H_{32}N_2O_2$·1.1HCl) C, H, N.

6-(*N,N*-Di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one *O*-Tosyloxime (14). Oxime **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 the mixture was stirred 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 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give 8.4 g of a dark oil. This was stripped with toluene (3 × 50 mL) to give a brown solid, which was dissolved in dry ether (150 mL). Addition of 1 N ethereal HCl and filtration gave the product as a hydrochloride salt. Recrystallization from 2-propanol/ether gave 5.6 g, 13 mmol (68%), mp 158 °C (dec). IR (KBr) 2961, 2410, 1370, 1190, 813 cm^{-1}; ^{1}H NMR (HCl-salt, CD$_3$OD) 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; ^{13}C NMR (CDCl$_3$) 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 (CI) *m/z* 419 (M+1); Anal.($C_{23}H_{34}N_2SO_3$·HCl) C, H, N, Cl.

Pharmacology. All compounds were tested as hydrochloride salts unless noted otherwise. All in vitro and in vivo experiments were performed at Pfizer Global Research & Development (Ann Arbor, MI).

In Vitro Receptor Binding Assays. Dopamine D$_1$ Receptors. Inhibition by compounds of the binding of 0.20 nM [^{3}H]SCH 23390 to dopamine D$_1$ receptors in membranes from rat striatum was determined as described by Hyttel et al.[20]

Dopamine D_2 Receptors. Inhibition by compounds of the binding of 0.50 nM [^{3}H]spiperone to dopamine D_2 receptors in membranes from rat striatum was determined as described by Hyttel et al.[21]

Functional Assays. The methods for determining the intrinsic activity of the compounds at the DA D_1 and D_2 receptor were adapted from those described by Sihdu et al. and Lajiness et al.[22,23]

The Ungerstedt Rat Rotation Model for Parkinson's Disease.[16] 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 μg of 6-hydroxydopamine HBr in 4 μL^{-1} saline with ascorbic acid 1 mg mL^{-1} added. After 3 weeks recovery, completeness of lesion was assessed with apomorphine 50 $\mu g\ kg^{-1}$ 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 rotorat 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 are presented as full rotations in contralateral directions. Rats were used once weekly.

Rats that were used for the blocking studies received 0.3 mg kg^{-1} haloperidol ip or 0.03 mg kg^{-1} SCH23390 ip, both or saline, 30 min prior to administration of 1.0 mg kg^{-1} po of (±)-**5**. Full contralateral rotations were recorded until 1 h after administration of (±)-**5**. The cumulative full contralateral rotations of saline pretreated rats were used as reference. The decrease in rotational behavior was calculated from the reference value and the cumulative full contralateral rotations of pretreated with haloperidol, SCH23390, or both.

References

(1) Johnson, S. J.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A.; Wise, L. D. Dihydro-analogues of 5- and 7-Hydroxy-2-aminotetralins: Synthesis and Dopaminergic Activity. In *Proceedings of the 208th American Chemical Society National Meeting*; American Chemical Society: Washington, DC, 1994; MEDI−P175.

(2) Dijkstra, D.; Venhuis, B. J.; Wikström, H. V.; Wise, L. D.; Wustrow, D. J.; Meltzer, L. T. Method for treating Parkinson's disease by administering of (−)-5-keto-2-N,N-di-propylaminotetrahydrotetralin. Patent, WO 0128977 A1, 2001.

(3) Venhuis, B. J.; Wikström, H. V.; Rodenhuis, N.; Sundell, S.; Wustrow, D.; Meltzer, L. T.; Wise, L. D.; Johnson, S. J.; Dijkstra, D. A New Type of Prodrug of Catecholamines − An Opportunity to Improve the Treatment of Parkinsons Disease. *J. Med. Chem.* **2002**, *45*, 2349−2351.

(4) Venhuis, B. J.; Dijkstra, D.; Wustrow, D. J.; Meltzer, L. T.; Wise, L. D.; Johnson, S. J.; Heffner, T. G.; Wikström, H. V. Orally Active Analogues of the Dopaminergic Prodrug 6-(*N*,*N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one. Synthesis and Pharmacological Activity. *J. Med. Chem.* **2003**, *46*, 584−590.

(5) Katerinopoulos, H. E.; Schuster, D. I. Structure−Activity Relationships for Dopamine Analogues: a Review. *Drugs Future* **1987**, *12*, 223−253.

(6) Rodenhuis, N.; Timmerman, W.; Wikström, H. V.; Dijkstra, D. Thiophene analogues of naphthoxazines and 2-aminotetralins: bioisosteres with improved relative oral bioavailability, as compared to 5-OH-DPAT. *Eur. J. Pharmacol* **2000**, *394*, 255−263.

(7) Glase, S. A.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. Synthesis and Dopaminergic Activity of Pyridine Analogues of 5-Hydroxy-2-(di-*n*-propylamino)tetralin. *J. Med. Chem.* **1995**, *38*, 3132−3137.

(8) Seiler, M. P.; Markstein, R. Further characterization of structural requirements for agonists at the striatal dopamine D_2 receptor and a comparison with those at the striatal dopamine D_1 receptor. Studies with a series of monohydroxyaminotetralins on acetylcholine release from rat striatum. *Mol. Pharmacol.* **1984**, *26*, 452−457.

(9) Seiler, M. P.; Stoll, A. P.; Closse, A.; Frick, W.; Jaton, A.; Vigouret, J. M. Structure−activity relationships of dopaminergic 5-hydroxy-2- aminotetralin derivatives with functionalized N-alkyl substituents. *J. Med. Chem.* **1986**, *29*, 912−917.

(10) Van der Weide, J.; De Vries, J. B.; Tepper, P. G.; Horn, A. S. Pharmacological profiles of three new, potent and selective dopamine receptor agonists: N-0434, N-0437 and N-0734. *Eur. J. Pharmacol.* **1986**, *125*, 173−282.

(11) Sakene, K.; Kawabata, K.; Inamoto, Y.; Yamanaka, H.; Takaya, T. Research and development of new oral cephems, cefixime and cefdinir. *Yakugaku Zasshi* **1993**, *113*, 605−626.

(12) Stanczyck, F. Z.; Roy, S. Metabolism of levonorgestrel, norethindron, and structurally related contraceptive steroids. *Contraception* **1990**, *42*, 67−96.

(13) Okamoto, Y.; Kiriyama, K.; Namiki, Y.; Matsushita, J.; Fulioka, M.; Yasuda, T. Degradation kinitics and isomerisation of cefdinir, a new oral cephalosporin, in aqueous solution. 1. *J. Pharm. Sci.* **1996**, *85*, 976−983.

(14) Wild, M. J.; Rudland, P. S.; Back, D. J. Metabolism of the oral contraceptive steroids ethynylestradiol and norgestimate by normal (Huma 7) and maligant (MCF-7 and ZR-75−1) human breast cells in culture. *J. Steroid Biochem. Mol. Biol.* **1990**, *39*, 535−543.

(15) Li, Q. G.; Humpel, M. Pharmacokinetics, hydrolysis and aromatization of norethistrerone-3-oxime in female cynomolgus monkey. *Eur. J. Drug Metab. Pharmacokinet.* **1992**, *17*, 281−291.

(16) Ungerstedt, U.; Arbuthnott, G. W. Quantitative recording of rotational behaviour in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. *Brain Res.* **1970**, *24*, 485−493.

(17) Venhuis, B. J. A New Type of Prodrug for the Treatment of Parkinson's Disease; In *Enone Prodrugs of Catecholamines − Orally Active Compounds as Potential anti-Parkinsonian Agents*; Rijksuniversiteit Groningen, The Netherlands, Thesis, 2002; pp 59−90.

(18) Weller, T.; Alig, L.; Berensini, M.; Blackburn, B.; Bunting, S.; Havárdy, P.; Hürzeler-Müller, M.; Knopp, D.; Levet-Trafit, B.; Lipari, M. T.; Modi, N. B.; Müller, M.; Refino, C. J.; Schmitt, M.; Schönholzer, P.; Weiss, S.; Steiner, B. Orally active fibrinogen Receptor antagonists. 2. Amidooximes as Prodrugs of Amidines. *J. Med. Chem.* **1996**, *39*, 3139−3147.

(19) Markham, A.; Benfield, P. Pergolide, a review of its Pharmacology and Therapeutic Use in Parkinson's Disease. *CNS Drugs Apr.* **1997**, *7*, 328−340.

(20) Hyttel, J.; Arnt, J. Characterization of binding of [3H]-SCH 23390 to dopamine D_1 receptors. Correlation to other D_1 and D_2 measures and effect of selective lesions. *J. Neurol. Transm.* **1987**, *68*, 171−189.

(21) Hyttel, J.; Larsen, J. J. Neurochemical profile of Lu-19−005, a potent inhibitor of uptake of dopamine, noradrenaline, and serotonine. *J. Neurochem.* **1985**, *44*, 1615−1622.

(22) Sidhu, A.; Fishman, P. H. Identification and characterization of functional D_1 dopamine receptors in a human neuroblastoma cell line. *Biochem. Biophys. Res. Commun.* **1990**, *166*, 574−579.

(23) Lajiness, M. E.; Chio, C. L.; Huff, R. M. D_2 dopamine receptor stimulation of mitogenesis in transfected Chinese hamster ovary cells: relationship to dopamine stimulation of tyrosine phosphorylations. *J. Pharmacol. Exp. Ther.* **1993**, *276*, 1573−1581.

JM0307786