

mp 118–119 °C; IR (CHCl₃) 1655 (C=O), 1595, cm⁻¹ (C=C); UV (log ε) 251 (4.19), 277 (4.04), 281 (4.04), 332 (3.30), 382 nm (3.01); ¹H NMR (CDCl₃) δ 1.85 (m, 2 H, H-3), 2.68 (dd, *J* = 6.0, 9.0 Hz, 2 H, H-4), 3.36 (s, 3 H, OCH₃), 4.49 (t, *J* = 6.0 Hz, 1 H, H-2), 7.65 (m, 2 H, Ar H), 8.10 (m, 2 H, Ar H); MS, *m/z* 244.0737 (M⁺, C₁₄H₁₂O₄ requires 244.0735).

2-Acetoxy-3-(2-propenyl)-1,4-naphthoquinone (16). In 1.0 mL of pyridine was placed 43 μL of acetic anhydride and to this was added 100 mg of 12. The resulting dark red solution was stirred overnight at room temperature. In the morning 25 mL of ether was added and the resulting solution was washed with 3 × 15 mL of 1.0 N HCl. The ether was dried (MgSO₄) and evaporated to give a residue, which was purified by column chromatography (CHCl₃) to give 87 mg (73%) of 16 as yellow crystals as a mixture of *cis* and *trans* isomers: mp 92–94 °C; IR (CCl₄) 1770 (ester C=O), 1660 (quinone C=O), 1625 (quinone C=O), 1590 (C=C), 1170 cm⁻¹ (C—O); ¹H NMR (CDCl₃) δ 1.86 (d, *J* = 6 Hz, 3 H, C=CCH₃), 2.32 (s, 3 H, COCH₃), 6.39 (m, 2 H, CH=CHCH₃), 6.80 (dm, *J* = 6 Hz, 1 H, C=CHCH₃), 7.64 (m, 2 H, Ar H), 8.00 (m, 2 H, Ar H). Anal. (C₁₅H₁₂O₄) C, H.

2-(Propionyloxy)-3-(2-propenyl)-1,4-naphthoquinone (17). To 1.0 mL of pyridine was added 48 μL of propionyl chloride and to this was added 100 mg of 12. The resulting dark red solution was allowed to stir for 1 h at room temperature. Initial attempts to remove the excess pyridine via an aqueous wash led to decomposition of the product. Therefore, the pyridine was removed under reduced pressure and the product was purified by column chromatography to give 10 mg (7.8%) of 17 as yellow crystals as a mixture of *cis* and *trans* isomers: mp 59–61 °C; IR (CCl₄) 1770 (ester C=O), 1670 (quinone C=O), 1630 (quinone C=O), 1595 cm⁻¹ (C=C); ¹H NMR (CDCl₃) δ 1.32 (t, *J* = 7 Hz, 3 H, CH₂CH₃), 1.98 (d, *J* = 6 Hz, 3 H, C=CCH₃), 2.74 (q, *J* = 7 Hz, 2 H,

COCH₃), 6.54 (brs, 1 H, CH=CHCH₃), 6.98 (dm, *J* = 7 Hz, 1 H, C=CHCH₃), 7.70 (m, 2 H, Ar H), 8.10 (m, 2 H, Ar H). Anal. (C₁₆H₁₄O₄) C, H.

2-(Benzyloxy)-3-(2-propenyl)-1,4-naphthoquinone (18) was similarly prepared with benzoyl chloride (63 μL) in 20% yield and isolated as yellow crystals as a mixture of *cis* and *trans* isomers: mp 118–120 °C; IR (CCl₄) 1740 (ester C=O), 1670 (quinone C=O), 1630 (quinone C=O), 1590 (C=C), 1110 cm⁻¹ (C—O); ¹H NMR (CDCl₃) δ 1.95 (d, *J* = 6 Hz, 3 H, CH₃), 6.36 (m, 1 H, CH=CHCH₃), 6.65 (m, 1 H, C=CHCH₃), 7.63 (m, 5 H, Ar H), 8.23 (m, 4 H, Ar H). Anal. (C₂₀H₁₄O₄) C, H.

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Registry No. 1, 6754-13-8; 2, 110271-41-5; 3, 110271-42-6; 4, 106261-83-0; 5, 83-72-7; 6-(*cis*), 110271-43-7; 6-(*trans*), 110271-44-8; 7, 110271-45-9; 8, 110271-46-0; 9, 110271-47-1; 10, 110271-48-2; 11, 110271-49-3; 12-(*cis*), 110271-50-6; 12-(*trans*), 110271-51-7; 13, 4512-56-5; 14, 17112-93-5; 15, 106261-85-2; 16, 49827-70-5; 17, 110271-52-8; 18, 110271-53-9; acrolein, 107-02-8; propionyl chloride, 79-03-8; benzoyl chloride, 98-88-4.

Carbamate Ester Derivatives as Potential Prodrugs of the Presynaptic Dopamine Autoreceptor Agonist (–)-3-(3-Hydroxyphenyl)-*N*-propylpiperidine

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Twenty derivatives bearing substituents on the phenolic function of (–)-3-(3-hydroxyphenyl)-*N*-propylpiperidine [(–)-3-PPP] were synthesized and tested as prodrugs. The carbamate ester derivatives were found to be the most suitable prodrugs, and especially the 4-isopropylphenylcarbamate **20** was capable of escaping the first-pass metabolism and still generating high plasma levels of the parent compound. Four hours after an oral dose of 100 μmol/kg to rats, a plasma level of 2400 nmol/L of (–)-3-PPP was detected by an HPLC method. This was 90 times the level reached after 4 h (27 nmol/L) when (–)-3-PPP itself was given orally at the same dose.

In our preclinical studies of the presynaptic dopamine autoreceptor agonist (–)-3-(3-hydroxyphenyl)-*N*-propylpiperidine [(–)-3-PPP], developed as an alternative antipsychotic agent in humans,¹ the intravenous administration of [³H]-(–)-3-PPP to mice resulted in high concentrations in the central nervous system (CNS) shortly after administration.² This indicated good penetration through the blood–brain barrier. We also found that (–)-3-PPP had a low oral bioavailability in all species investigated. Following oral administration in rats, the major portion of the dose (89%) was excreted in the urine as the 3-PPP-glucuronide, which indicated that the compound was well absorbed. The reduced systemic availability

following oral administration was thus due to first-pass metabolism in the intestinal mucosa and/or in the liver.

In this paper we describe the synthesis and the evaluation of a number of prodrug derivatives of (–)-3-PPP. Our aim was to design derivatives with good absorption, capable of escaping the first-pass metabolism in the hepatoportal system, and generating high plasma and tissue levels of the parent compound, (–)-3-PPP. For this purpose, a screening system was designed where rats were given 100 μmol/kg orally of the prodrug, whereupon the plasma levels of the parent compound were determined after 1 and 4 h.

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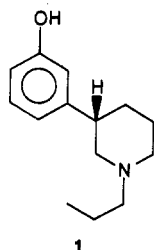
Table I

Compound		M.p °C	$[\alpha]_D^{20}$	Yield %	Formulae	Analyses
1	H	185–187	-7.1°		$C_{14}H_{21}NO \times HCl$	CHNO
2	$CH_3(CH_2)_8CO-$	142–144	-5.56°	63	$C_{24}H_{39}NO_2 \times HCl$	CHNO
3	$CH_3-O-CH_2-CH_2-O-CH_2-$	136–137	-29.3°	60	$C_{18}H_{29}NO_3 \times (COOH)_2$	CHNO
4		87–92	racemate	90	$C_{20}H_{24}N_2O_2 \times (COOH)_2$	CHO
5		oil ^a	racemate	30	$C_{25}H_{32}N_2O_4$ base	
6	$(C_2H_5O)_2PO-$	hygroscopic	racemate	81	$C_{18}H_{30}PNO_4 \times (COOH)_2$	CHPN
7	$(CH_3)_3C-CO-$	155–157	racemate	73	$C_{19}H_{29}NO_2 \times HCl$	CHO
8	$(CH_3)_2N-CO-$	181–182	racemate	71	$C_{17}H_{26}N_2O_2 \times HCl$	CHO
9		171	racemate	52	$C_{21}H_{27}NO \times HCl$	CHO
10		194–195	-8.0°	60	$C_{21}H_{26}N_2O_2 \times HCl$	CHO
11	$CH_3-CH_2-CH_2-NH-CO-$	186–188	-7.85°	75	$C_{18}H_{28}N_2O_2 \times HCl$	CHNO
12	$(CH_3)_2CH-NH-CO-$	184–185	-6.91°	80	$C_{18}H_{28}N_2O_2 \times HCl$	CHNO
13	$(CH_3)_3C-NH-CO-$	179–181	-3.05°	77	$C_{19}H_{30}N_2O_2 \times HCl$	CHO
14	$[(CH_3)_2CH]_2N-CO-$	193–195	-5.6°	16	$C_{21}H_{34}N_2O_2 \times HCl$	CHO
15		209–210	-8.3°	57	$C_{20}H_{30}N_2O_2 \times HCl$	CHO
16		191–193	-90.5°	87	$C_{23}H_{30}N_2O_2 \times HCl$	CHNO
17		170–171	+80.0°	82	$C_{23}H_{30}N_2O_2 \times HCl$	CHNO
18		205–208	-5.20°	48	$C_{21}H_{25}N_2O_2Cl \times HCl$	CHNO
19		191–193	-1.64°	56	$C_{23}H_{30}N_2O_3 \times HCl$	CHNO
20		193–194	-1.54°	25	$C_{24}H_{32}N_2O_2 \times HCl$	CHNO
21		183–184	-1.28°	61	$C_{23}H_{30}N_2O_4 \times HCl$	CHNO

^a Characterized by MS and purity was checked by HPLC (Purity: 99.4 %)

Chemistry

All of the compounds were derivatives bearing substituents on the phenolic function of the 3-PPP (1) molecule.



The acyl ester derivatives 2, 4, and 7 were prepared from their corresponding acid chloride derivatives and the free base of 3-PPP, with pyridine as the base and in some cases also as the solvent. The protected amino acid used as starting material for compound 5 was converted to its acid chloride in situ with $POCl_3$. Synthesis of the phosphate ester 6 from diethyl chlorophosphate, as well as the car-

bamate derivative 8 from dimethylcarbamoyl chloride, was carried out with the hydrochloride salt of 3-PPP with potassium carbonate as base. Preparation of the diisopropylcarbamate derivative 14 was achievable from the carbamoyl chloride in poor yield by using TEA as the base, but the synthesis failed when pyridine was used as the base in analogy with compound 15. For preparation of the two "ether" derivatives 3 and 9, stronger bases, such as sodium hydride or potassium *tert*-butoxide, were used. A general and convenient method for the preparation of most of the carbamate derivatives was performed by heating the free base of 3-PPP with the appropriate isocyanate in toluene.³

Assay Method

Sprague-Dawley rats were given a solution of the prodrugs in distilled water at a standard dose of 100 μ mol/kg orally. Blood samples were collected in heparinized glass

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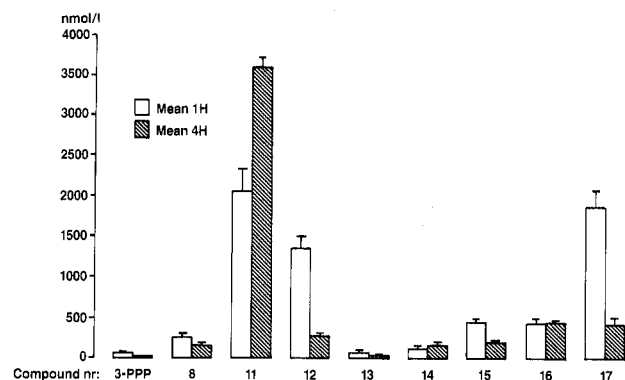


Figure 1. Concentrations of parent compound [(-)-3-PPP] in plasma 1 and 4 h after oral administration of 100 $\mu\text{mol/kg}$ of the alkyl carbamate ester to rats (mean of three to four rats and SD is indicated).

tubes after 1 and 4 h, and the plasma was analyzed for (-)-3-PPP by HPLC (for further details see the Experimental Section).

Results and Discussion

The initial nine compounds were synthesized with a large variability in the structures of the substituents (see Table I). This allowed us to test the potential of different phenolic derivatives as putative prodrugs.

The standard dose of the parent compound 1 given orally to rats gave a mean plasma concentration of 61 nmol/L after 1 h and 27 nmol/L after 4 h. Of the initially synthesized nine prodrug candidates 2–10, only the two carbamate derivatives 8 (Figure 1) and 10 (Figure 2) were able to generate increased plasma concentrations of (-)-3-PPP. The failure of some of the prodrug candidates to generate the parent compound in plasma may have many different explanations. The prodrug might have been too unstable and therefore hydrolyzed to the parent compound while in the gastrointestinal tract. This might have been the case for the acid-sensitive acyl ester derivative 2 and the "ether" derivative 3. The prodrug may also be poorly absorbed and/or resistant to hydrolysis to the parent compound.

The encouraging observations with the carbamate derivatives 8 and 10 made us further investigate these two classes of prodrug candidates, i.e., the alkylcarbamates and the arylcarbamates.

Several attempts have been made by other investigators^{4,5,6} to increase the lipid solubility of various CNS-active amines by using carbamate derivatives as prodrugs. Limited success has been achieved with carbamate derivatives of the amino function mainly because these prodrugs appear to be too resistant to cleavage to the parent active drug.⁷ Phenolic carbamate derivatives have been reported⁸ to generate the parent drug more easily. However, the chosen carbamate must not only have a rate of conversion to the parent drug which is faster than the sum of the rates of elimination of the unchanged prodrug and parent drug, but it also must be devoid of undesired pharmacological effects. As seen from Figure 1, compound 11 is one of the best prodrug candidates with regard to high

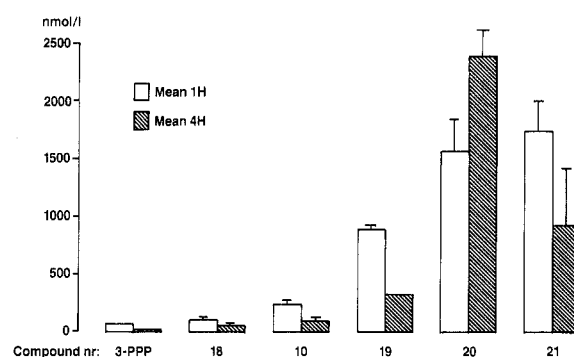


Figure 2. Concentrations of parent compound [(-)-3-PPP] in plasma 1 and 4 h after oral administration of 100 $\mu\text{mol/kg}$ of each aryl carbamate ester to rats (mean of three to four rats and SD is indicated).

plasma levels of parent drug. However, we also found that compounds 8, 11, 12, 16, and 17 caused convulsions in the rats. Some carbamates have been reported to be good insecticides,³ and the proposed mechanism of action for this effect is their interaction with acetylcholinesterase. Therefore, compound 12 was tested for this activity. The IC_{50} value for inhibition of acetylcholinesterase in human blood⁹ was found to be 10 μM , which indicated that compound 12 was not a potent enzyme blocker. Nevertheless, even a weak inhibition might still be attributed to the observed undesired effect if the concentration is high enough. It cannot be stated definitively from the data presented that high levels of (-)-3-PPP itself cannot be associated with convulsions. However, our initial pharmacokinetic studies showed that plasma levels above 10,000 nmol/L did not cause any signs of undesired effects. It is therefore most likely that the convulsions seen with some of the carbamate ester derivatives are caused by the prodrug and not by (-)-3-PPP.

Compounds 8, 14, and 15 were all examples of tertiary carbamate derivatives that appeared to be poor prodrugs of (-)-3-PPP. Interestingly, studies with the two diastereomers (*S,S*)-16 and (*R,S*)-17 indicated a different rate in the release of the parent compound.

As seen from Figure 2, the substituents in the phenyl ring of the aromatic carbamate derivatives have a crucial influence on the levels of (-)-3-PPP in plasma. None of these derivatives displayed convulsions or any other side effects. The *p*-chloro-substituted compound 18 gave lower plasma levels of the parent drug compared to the unsubstituted phenylcarbamate 10. However, more electron-donating substituents as in compounds 19, 20, and 21 strongly enhanced the levels of (-)-3-PPP in plasma. For instance, 1 h after the administration of prodrug 20, the plasma levels of (-)-3-PPP were 25 times higher than the levels obtained after the administration of (-)-3-PPP itself. This ratio was even larger (90 times) if plasma levels were compared 4 h after administration. Plasma levels of (-)-3-PPP after subcutaneous administration have previously been reported.¹¹ A dose of 30 $\mu\text{mol/kg}$ gave a plasma level of approximately 2500 nmol/L 1 h after dose. After 4 h the plasma level was only about 100 nmol/L. The prodrugs reported here have thus improved the systemic

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availability of (-)-3-PPP considerably.

In conclusion, prodrugs based on aryl carbamate derivatives of (-)-3-PPP have so far proven quite successful in achieving our goals. If a low bioavailability is the only limiting factor for the future development of this compound to a useful antipsychotic agent in humans,¹⁰ our data have shown that a substituted aryl carbamate prodrug may offer a suitable solution to this problem.

Experimental Section

Chemistry. Melting points were obtained on a Mettler FP 61 apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 457 IR spectrophotometer, and the optical rotations were determined on a Lambda Polarimeter AA-100. Mass spectrometry was performed on a LKB 9000 instrument at 70 eV with EI or FAB detector. The elemental analyses were performed by Elementeranalytjänst, Chemical Center, Lund, Sweden, or by Analytische Laboratorien Elbach, Engelskirchen, West Germany, and were within $\pm 0.4\%$ of the theoretical values. The purity was determined on a reversed-phase HPLC system with a Nucleosil C₁₈ column with phosphate buffer (pH 2.0)/methanol (mixed 55:45) as the mobile phase.

(-)-3-[3-(Decanoyloxy)phenyl]-N-propylpiperidine (2). Decanoyl chloride (1.20 g, 5.86 mmol) and pyridine (0.51 g, 6.32 mmol) in CH₂Cl₂ (15 mL) were added to a suspension of (-)-3-(3-hydroxyphenyl)-N-propylpiperidine hydrochloride (1) (1.50 g, 5.86 mmol) in CH₂Cl₂ (15 mL). The mixture was heated at reflux overnight. After cooling, the reaction mixture was diluted with CH₂Cl₂ and washed with aqueous NaOH (0.1 M) and then with water. The organic phase was dried (MgSO₄) and evaporated. The residual oil was converted into the hydrochloride salt and was recrystallized once from acetone: yield 1.65 g (63%); mp 142–144 °C; MS (70 eV), *m/z* 373 (5), 344 (100); [α]_D²⁰ -5.56° (c 1.8, MeOH). Anal. (C₂₄H₄₀NO₂Cl) C, H, N, O.

(-)-3-[3-[(Methoxyethoxy)methoxy]phenyl]-N-propylpiperidine (3). Sodium hydride (0.2 g, 5.9 mmol) was added portionwise to an ice-cooled suspension of 1 (1.5 g, 5.9 mmol) in THF (50 mL) under N₂ protection. Stirring was continued at 0 °C for 1 h. (Methoxyethoxy)methyl chloride (1.17 g, 9.4 mmol) was added dropwise, and the mixture was stirred for 1 h at 0 °C and 2 h at room temperature. The precipitated salt was filtered, and the residual solution was evaporated. Crystals were obtained as the oxalate salt, which was recrystallized from acetone: yield 1.4 g (60%); mp 136–137 °C; MS (70 eV), *m/z* 307 (70), 278 (100); [α]_D²⁰ -29.3° (c 2.1, MeOH). Anal. (C₂₀H₃₁NO₇) C, H, N, O.

3-[3-[(4-Pyridinylcarbonyl)oxy]phenyl]-N-propylpiperidine (4). Pyridine-4-carboxylic acid chloride (0.61 g, 4.3 mmol) in pyridine (0.34 g, 4.3 mmol) was added to a mixture of (±)-3-(3-hydroxyphenyl)-N-propylpiperidine hydrobromide (1.3 g, 4.3 mmol) and pyridine (0.34 g, 4.3 mmol) in CH₂Cl₂ (4 mL) at 0 °C. Stirring was continued at 40 °C overnight. The solvent was evaporated, and the residue was dissolved in ether and washed with aqueous NaOH (0.1 M). The dried (Na₂SO₄) organic phase was evaporated, and the residual oil was converted into its oxalate salt and recrystallized from 2-propanol: yield 1.25 g (90%); mp 87–92 °C. Anal. (C₂₂H₂₆N₂O₆) C, H, O.

3-[3-[2-(carbobenzoxymino)propanoyl]oxy]phenyl]-N-propylpiperidine (5). A solution of 2-(carbobenzoxymino)propanoic acid (0.89 g, 4.0 mmol) in THF (5 mL) was added to (±)-3-(3-hydroxyphenyl)-N-propylpiperidine base (0.87 g, 4 mmol) and phosphorus oxychloride (0.61 g, 4 mmol) in THF (10 mL), and the mixture was cooled to -15 °C. Pyridine (0.63 g, 8 mmol) was dissolved in THF (5 mL) and added dropwise during 10 min. Stirring was continued at room temperature overnight. The solvent was evaporated without heating (below 10 °C), and the residue was dissolved in CH₂Cl₂ and extracted with NaHCO₃ (0.5 M). The organic phase was evaporated, and the residual oil was purified on a silica gel column with CH₂Cl₂-methanol (85:15) as eluent: yield 0.5 g (30%) as base; MS-DI (70 eV), *m/e* 424 (5), 395 (90).

3-[3-(Diethylphosphono)phenyl]-N-propylpiperidine (6). A mixture of diethyl chlorophosphate (0.78 g, 4.5 mmol), (±)-3-(3-hydroxyphenyl)-N-propylpiperidine hydrochloride (1.0 g, 3.9 mmol), and potassium carbonate (2.23 g, 16.2 mmol) in CH₃CN (30 mL) was stirred at room temperature for 15 h. The precipitate

was filtered off, and the filtrate was evaporated. The crude residual oil was dissolved in CH₂Cl₂ and washed with NaHCO₃ (0.5 M). The organic phase was dried (Na₂SO₄) and evaporated: yield 1.12 g (81%) as base. The crystalline oxalate salt was hygroscopic: MS (70 eV), *m/z* 355 (78), 326 (100). Anal. (C₂₀H₃₂PNO₆) C, H, P, N.

3-[3-[(Trimethylacetyl)oxy]phenyl]-N-propylpiperidine (7). This compound was prepared according to the method described for compound 2 from trimethylacetyl chloride (1.20 g, 10 mmol), pyridine (0.87 g, 11 mmol), and (±)-3-(3-hydroxyphenyl)-N-propylpiperidine hydrochloride (2.55 g, 10 mmol): yield 2.47 g (73%); recrystallized from acetone, mp 155–157 °C. Anal. (C₁₉H₃₀NO₂Cl) C, H, O.

3-[3-[(Dimethylcarbamoyl)oxy]phenyl]-N-propylpiperidine (8). A solution of dimethylcarbamoyl chloride (1.07 g, 10 mmol) in CH₂Cl₂ (5 mL) was added to a suspension of powdered K₂CO₃ (3.45 g, 25 mmol) and (±)-3-(3-hydroxyphenyl)-N-propylpiperidine hydrochloride (2.5 g, 10 mmol) in CH₂Cl₂ (20 mL). The mixture was heated to reflux during 15 h. The precipitated salt was filtered off, and the solvent was evaporated. The residual oil was dissolved in ether, and white crystals were obtained after addition of HCl-saturated ether. Filtration and recrystallization from acetonitrile gave the desired compound: yield 2.3 g (71%); mp 181–182 °C. Anal. (C₁₇H₂₇N₂O₂Cl) C, H, O.

3-[3-(Benzyloxy)phenyl]-N-propylpiperidine (9). A mixture of (±)-3-(3-hydroxyphenyl)-N-propylpiperidine hydrobromide (1.0 g, 0.0033 mol), potassium *tert*-butoxide (1.0 g, 0.009 mol), and benzyl chloride (1.0 g, 0.009 mol) in *tert*-butyl alcohol (25 mL) was refluxed for 1 h. Water was added, and the mixture was extracted with ether. The organic phase was dried with Na₂SO₄ and evaporated to dryness, giving a pale yellow oily residue. The residue was chromatographed on a silica gel column with methanol as eluant. The pertinent fractions were collected and evaporated to dryness. The oily residue was dissolved in ether and HCl-saturated ether was added, giving white crystals. Evaporation and treatment of the residue with acetone gave 0.60 g (52%) of the desired product as white crystals: mp 171 °C. Anal. (C₂₁H₂₇NOCl) C, H, O.

(-)-3-[3-[(Phenylcarbamoyl)oxy]phenyl]-N-propylpiperidine (10). A mixture of (-)-3-(3-hydroxyphenyl)-N-propylpiperidine base (0.55 g, 2.5 mmol) and phenyl isocyanate (5.45 g, 4.6 mmol) in toluene (40 mL) was refluxed for 4 h. The solution was evaporated, and the residues were dissolved in ether. White crystals were obtained after addition of HCl-saturated ether: yield 0.56 g (60%) after recrystallization from acetonitrile; mp 194–195 °C; [α]_D²⁰ -8.0° (c 1.9, MeOH). Anal. (C₂₁H₂₇N₂O₂Cl) C, H, O.

(-)-3-[3-[(Propylcarbamoyl)oxy]phenyl]-N-propylpiperidine (11). A mixture of (-)-3-(3-hydroxyphenyl)-N-propylpiperidine base (3.0 g, 13.7 mmol) in toluene (40 mL) and propyl isocyanate (2.34 g, 27.4 mmol) was refluxed for 4 h. The solution was evaporated, and the residue was dissolved in ether and converted to the hydrochloride salt by addition of HCl-saturated ether. Filtration and recrystallization from acetonitrile gave the desired compound: yield 3.5 g (75%); mp 186–188 °C; [α]_D²⁰ -7.85° (c 2.1, MeOH). Anal. (C₁₈H₂₉N₂O₂Cl) C, H, N, O.

(-)-3-[3-[(Isopropylcarbamoyl)oxy]phenyl]-N-propylpiperidine (12). This compound was prepared from isopropyl isocyanate as described for compound 11: yield 80% as the hydrochloride salt after crystallization from 2-propanol-ether; mp 184–185 °C; MS (70 eV), *m/z* 304 (7), 190 (100); [α]_D²⁰ -6.91° (c 2.2; MeOH); IR 1700 (C=O) cm⁻¹. Anal. (C₁₈H₂₉N₂O₂Cl) C, H, N, O.

(-)-3-[3-[(2,2-Dimethylethyl)carbamoyl]oxy]phenyl]-N-propylpiperidine (13). This compound was prepared from pivaloyl isocyanate as described for compound 11: yield 77%. The hydrochloride salt was recrystallized from 2-propanol-ether: mp 179–181 °C; MS (70 eV), *m/z* 318 (4), 190 (100); [α]_D²⁰ -3.05° (c 1.1, MeOH); IR 1700 (C=O) cm⁻¹. Anal. (C₁₈H₃₁N₂O₂Cl) C, H, O.

(-)-3-[3-[(Diisopropylcarbamoyl)oxy]phenyl]-N-propylpiperidine (14). A mixture of diisopropylcarbamoyl chloride (3.73 g, 23 mmol), (-)-3-(3-hydroxyphenyl)-N-propylpiperidine base (2.0 g, 9.1 mmol), and triethylamine (1.84 g, 18 mmol) in CH₂Cl₂ (30 mL) was heated to reflux for 17 h. The solvent was evaporated

and substituted with ether. The precipitate was filtered off, and the desired compound was isolated from the filtrate by addition of HCl-saturated ether. Two recrystallizations from acetonitrile gave the pure hydrochloride salt: yield 0.55 g (16%); mp 193–195 °C; MS (70 eV), m/z 346 (8), 317 (100); $[\alpha]_D^{20}$ -5.6° (c 1.6, MeOH). Anal. ($C_{21}H_{35}N_2O_2Cl$) C, H, O.

(-)-3-[3-[(Piperidylcarbonyl)oxy]phenyl]-*N*-propylpiperidine (15). A solution of 1-piperidinecarboxylic acid chloride (4.03 g, 27.3 mmol) and (-)-3-(3-hydroxyphenyl)-*N*-propylpiperidine base (2.0 g, 9.1 mmol) in pyridine (25 mL) was stirred at 60 °C for 4 h. The pyridine was evaporated carefully. The residue crystallized during washing with ether and tetrahydrofuran. Recrystallization from acetonitrile afforded the desired product as hydrochloride salt: yield 1.7 g (57%); mp 209–210 °C; MS-DI (70 eV), m/z 330 (6), 301 (100); $[\alpha]_D^{20}$ -8.3° (c 2.1, MeOH); IR 1720 (C=O) cm^{-1} . Anal. ($C_{26}H_{31}N_2O_2Cl$) C, H, O.

(*S,S*)-(-)-3-[3-[(1-Phenylethyl)carbamoyl]oxy]phenyl]-*N*-propylpiperidine (16). A mixture of (*S*)-(-)-1-phenylethyl isocyanate (2.68 g, 18.3 mmol) and (*S*)-(-)-3-(3-hydroxyphenyl)-*N*-propylpiperidine base (2.0 g, 9.1 mmol) in toluene (40 mL) was heated at reflux temperature for 3 h. The clear solution was evaporated, and the residual oil was dissolved in ether and converted to its crystalline hydrochloride salt. Recrystallization from butyl acetate–butanol gave the pure desired compound: yield 3.22 g (87%); MS-DI (70 eV), m/z 366 (2), 190 (100); $[\alpha]_D^{20}$ -90.5° (c 2.7, MeOH). Anal. ($C_{23}H_{31}N_2O_2Cl$) C, H, N, O.

(*R,S*)-(+)-3-[3-[(1-Phenylethyl)carbamoyl]oxy]phenyl]-*N*-propylpiperidine (17). This compound was prepared as described for compound 16 from (*R*)-(+)-1-phenylethyl isocyanate: yield 3.0 g (82%); mp 170–171 °C; MS-DI (70 eV), m/z 366 (1), 190 (100); $[\alpha]_D^{20}$ +80.0° (c 2.6, MeOH). Anal. ($C_{23}H_{31}N_2O_2Cl$) C, H, N, O.

(-)-3-[3-[(4-Chlorophenyl)carbamoyl]oxy]phenyl]-*N*-propylpiperidine (18). This compound was prepared as described for compound 10 from 4-chlorophenyl isocyanate: yield 48% after recrystallization from acetonitrile; mp 205–208 °C; MS-DI (70 eV), m/z 153 (100), 155 (33), 219 (36); $[\alpha]_D^{20}$ -5.20° (c 1.57, MeOH); IR 1685 (C=O) cm^{-1} . Anal. ($C_{21}H_{26}N_2O_2Cl_2$) C, H, N, O.

(-)-3-[3-[(4-Ethoxyphenyl)carbamoyl]oxy]phenyl]-*N*-propylpiperidine (19). This compound was prepared as described for compound 10 from 4-ethoxyphenyl isocyanate: yield 56% after recrystallization from acetonitrile; mp 191–193 °C; MS-DI (70 eV), m/z 190 (100), 135 (48), 219 (11); $[\alpha]_D^{20}$ -1.64° (c 1.46, MeOH); IR 1720 (C=O) cm^{-1} . Anal. ($C_{23}H_{31}N_2O_3Cl$) C, H, N, O.

(-)-3-[3-[(4-Isopropylphenyl)carbamoyl]oxy]phenyl]-*N*-propylpiperidine (20). This compound was prepared as described for compound 10 from 4-isopropylphenyl isocyanate in 25% yield after recrystallization twice from acetonitrile: mp 193–194 °C; MS, m/z 380 (1.2), 190 (100); $[\alpha]_D^{20}$ -1.54° (c 1.49, MeOH). Anal. ($C_{24}H_{33}N_2O_2Cl$) C, H, N, O.

(-)-3-[3-[(3,4-Dimethoxyphenyl)carbamoyl]oxy]phenyl]-*N*-propylpiperidine (21). This compound was pre-

pared as described for compound 10 from 3,4-dimethoxyphenyl isocyanate: yield 61% after recrystallization from butyl acetate–butanol; mp 183–184 °C; MS-DI (70 eV), m/z 369 (1.8), 190 (100); $[\alpha]_D^{20}$ -1.28° (c 1.32, MeOH). Anal. ($C_{23}H_{31}N_2O_4Cl$) C, H, N, O.

Bioavailability Test Procedure. Sprague–Dawley rats (male, weight 230–270 g), fasted overnight before the experiment and then were administered 100 μ mol/kg of each substance as a water solution (4 mL/kg) by oral gavage. Blood samples were taken under light diethyl ether anesthesia via the orbital venous plexus into heparinized glass tubes after 1 and 4 h. The samples were immediately chilled on ice and centrifuged (100 g for 10 min) to separate the plasma. Plasma samples were stored frozen at -70 °C until analysis. (-)-3-PPP and prodrugs were extracted from the plasma samples to an organic phase of hexane–diethyl ether–butanol (70:25:5) at pH 8.5 (isoelectric point for the parent compound). After evaporation with N_2 , the residue was dissolved in phosphate buffer (pH 2) and assayed by reversed-phase HPLC. A Microsphere (100 \times 4.6 mm, C18, 3 μ m) column was used, and the flow rate of the mobile phase (phosphate buffer pH 2) was 0.7 mL/min. The parent compound was detected electrochemically with a LC 4B Amperometric detector. A batch of control samples and standard solutions were prepared before each experiment and kept frozen at -70 °C. Three control samples were analysed on each day of operation.

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Registry No. 1-HCl, 88768-67-6; 2, 110222-35-0; 2-HCl, 88768-71-2; 3, 110174-82-8; 3-(CO₂H)₂, 110174-96-4; (\pm)-4, 110174-83-9; (\pm)-4-(CO₂H)₂, 110174-97-5; (\pm)-5 (isomer 1), 110174-84-0; (\pm)-6, 110174-85-1; (\pm)-6-(CO₂H)₂, 110174-98-6; (\pm)-7, 110174-86-2; (\pm)-7-HCl, 110174-99-7; (\pm)-8, 110174-87-3; (\pm)-8-HCl, 110175-00-3; (\pm)-9, 110174-88-4; (\pm)-9-HCl, 110175-01-4; 10, 110174-89-5; 10-, 110174-89-5; 11, 99155-91-6; 11-HCl, 110175-03-6; (\pm)-5 (isomer 2), 110175-14-9; 12, 99155-96-1; 12-HCl, 110175-04-7; 13, 99155-97-2; 13-HCl, 110175-05-8; 14, 99155-92-7; 14-HCl, 110175-06-9; 15, 99155-93-8; 15-HCl, 110175-07-0; 16, 110174-90-8; 16-HCl, 110175-08-1; 17, 110174-91-9; 17-HCl, 110175-09-2; 18, 99155-95-0; 18-HCl, 110175-10-5; 19, 110174-92-0; 19-HCl, 110175-11-6; 20, 110174-93-1; 20-HCl, 110175-12-7; 21, 99155-94-9; 21-HCl, 110175-13-8; H₃C(CH₂)₃COCl, 112-13-0; H₃CO(CH₂)₂O-CH₂Cl, 3970-21-6; (\pm)-C₆H₅CH₂O₂CNHCH(CH₃)CO₂H, 4132-86-9; (C₂H₅O)POCl, 814-49-3; (H₃C)₃CCOCl, 3282-30-2; (H₃C)₂NCOCl, 79-44-7; C₆H₅CH₂Cl, 100-44-7; C₆H₅NCO, 103-71-9; H₃C(CH₂)₂-NCO, 110-78-1; (H₃C)₂CHNCO, 1795-48-8; (H₃C)₃CNCO, 4461-20-5; [(H₃C)₂CH]₂NCOCl, 19009-39-3; (*S*)-C₆H₅CH(CH₃)NCO, 14649-03-7; (*R*)-C₆H₅CH(CH₃)NCO, 33375-06-3; 4-ClC₆H₄NCO, 104-12-1; 4-C₂H₅OC₆H₄NCO, 32459-62-4; 4-(H₃C)₂CHC₆H₄NCO, 31027-31-3; 3,4-(H₃CO)₂C₆H₃NCO, 37527-66-5; pyridine-4-carboxylic acid chloride, 14254-57-0; 1-piperidinecarboxylic acid chloride, 13939-69-0; (\pm)-3-(3-hydroxyphenyl)-*N*-propylpiperidine hydrobromide, 110174-94-2; (\pm)-3-(3-hydroxyphenyl)-*N*-propylpiperidine, 83228-38-0; (\pm)-3-(3-hydroxyphenyl)-*N*-propylpiperidine hydrochloride, 110174-95-3.