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

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A series of analogues of 6-(*N*,*N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (**6**), an enone prodrug of the mixed DA D_1/D_2 agonist 5,6-diOH-DPAT (**2**), was synthesized. The pharmacological profiles of these new enones and their in vivo pharmacological activities were investigated in the Ungerstedt rat rotation model for Parkinson's disease. At 0.1 mg kg^{-1} po, the *N*-methyl-*N*-*n*-propyl (**12**) and the *N*-ethyl-*N*-propyl (**13**) analogues induced pronounced and long lasting pharmacological effects. The pharmacological profile of enone **12** was found to be similar to that of **6**, while enone **13** was significantly more potent than **6** ($p < 0.01$). Analyses of rat brains after the administration of (−)-**6** and **13** indicated the presence of hydroxylated metabolites of the parent enones. It is speculated that such metabolites are α′-hydroxylated enones that may constitute the first step in the formation of the corresponding catechols.

Introduction

The potential utility of the directly acting dopamine (DA) D_2 agonist *S*-5-hydroxy-2-(di-*n*-propylamino)tetralin (*S*-(−)-5-OH-DPAT, (−)-**1**) and the mixed DA D_1/D_2 agonist *S*-(−)-5,6-dihydroxy-2-(di-*n*-propylamino)tetralin (*S*-(−)-5,6-diOH-DPAT, (−)-**2**) in the treatment of Parkinson's disease has previously been indicated (Figure 1).[1−6] However upon oral administration, the phenol and the catechol moieties are rapidly metabolized to an extent that limits the therapeutic usefulness of these compounds.[7] For instance, the potential anti-Parkinson compound (−)-N-0923 ((−)-**3**) undergoes extensive first-pass metabolism (glucuronidation).[8,9] In the past, circumvention of this problem was attempted by developing prodrugs. Common prodrugs of phenols and catechols are esters and carbamates.[10−15] Less common are, for example, ether derivatives as reported for (±)-**4**.[8] These types of prodrugs generally do not improve the in vivo characteristics sufficiently to make oral administration feasible. For instance, the diacetyl ester prodrug ABT-431 (**5**) has a plasma half-life for both esters of 60 s and is only efficacious as DA D_1 agonist after intravenous (iv) administration.[16]

Recently, we described the synthesis and pharmacological evaluation of *S*-(−)-6-(*N*,*N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one ((−)-**6**), an orally active prodrug of the mixed DA D_1/D_2 agonist (−)-**2** (Scheme 1).[17−19] This prodrug was found to be efficacious in vivo in models for Parkinson's disease in the rat. Because many *N*-(alkylhydroxy)-2-aminotetralins are known to act as DA agonists (Table 1), we decided to synthesize a series of racemic analogues of **6** with different N-substituents.[4,5,20] Further, a fluorinated analogue of **6** was prepared as a potential ligand for positron emission tomography (PET), aiming at a phar-

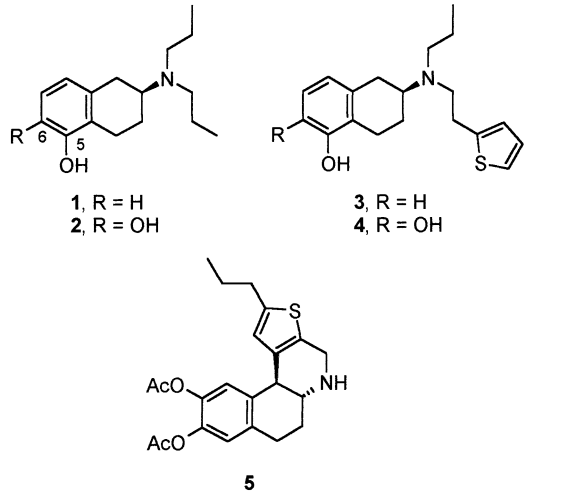

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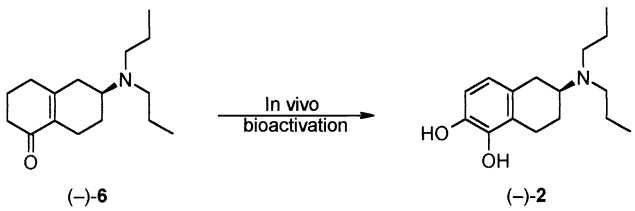
Figure 1. Structures of some hydroxylated 2-aminotetralin DA receptor agonists; *S*-(−)-5-OH-DPAT ((−)-**1**), *S*-(−)-5,6-diOH-DPAT ((−)-**2**), (−)-N-0923 ((−)-**3**), *S*-(−)-5,6-diOH−PTAT ((−)-**4**), and ABT-431 (**5**).

Scheme 1[a]



(−)-**6** (−)-**2**

[a] Bioactivation of (−)-**6** to (−)-**2**.

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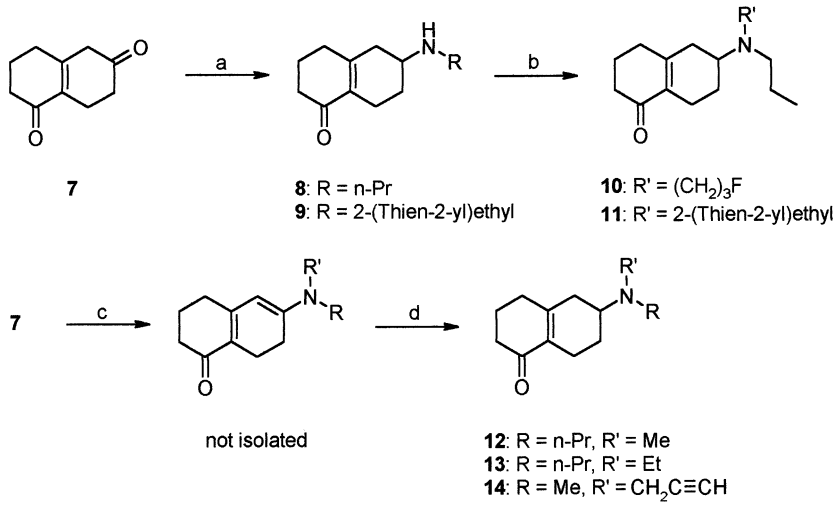
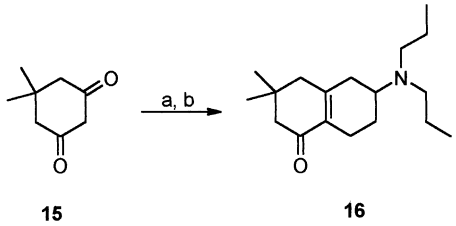
Scheme 2[a]



[a] Reagents and conditions: (a) RNH_2, $NaBH_3CN$, THF/AcOH, 0 °C; (b) propionaldehyde, $NaBH_3CN$, THF/AcOH, 0 °C or $F(CH_2)_3Br$, Cs_2CO_3, acetonitrile, 80 °C; (c) RR′NH, toluene, 60 °C; (d) $NaBH_3CN$, THF/AcOH, 0 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) (i) $(CH_2O)_n$, Pr_2NH, toluene, 85 °C; (ii) acetone, toluene, 85 °C; (b) $NaBH_3CN$, THF/AcOH, 0 °C − rt.

Table 1. Binding Affinities of Some Hydroxylated Aminoteralins for the DA D_1 and DA D_2 Receptor (nM)[a]

compound	N-substituents		K_i, D_1	K_i, D_2
(−)-**1**[b]	n-Pr	n-Pr	1.1	3[37]
(−)-**2**[b]	n-Pr	n-Pr	3	2[37]
(±)-**3**	n-Pr	2-(thien-2-yl)ethyl	500	15[9]
(±)-**4**	n-Pr	2-(thien-2-yl)ethyl	110	6[9]

[a] From calf striatal homogenates using [^{3}H]SCH 23390 (D_1) and [^{3}H]N-0437 (D_2). [b] High affinity binding only.

macological effect similar to that of **6**. Since the enone ring of (−)-**6** is aromatized in the bioactivation process, an analogue was prepared, in which this aromatization process is likely to be affected. All of the newly synthesized enones were pharmacologically evaluated in vivo in the Ungerstedt rat rotation model for Parkinson's disease.[21] To investigate the presence of metabolites, brain extracts of rats treated with enone prodrugs were analyzed.

Chemistry

The syntheses of the new enones are outlined in Schemes 2 and 3. The 1,6-diketone precursor **7** was prepared in three steps according to literature procedures.[22−25] Reductive amination of **7** in tetrahydrofuran, in the presence of 1 equiv of acetic acid, proceeded cleanly to give **8** and **9** which were used without further purification because they were found to decompose upon standing (Scheme 2). Secondary amine **8** was alkylated with 3-fluoropropyl 1-bromide in acetonitrile with Cs_2CO_3 and KI to give enone **10** in moderate yield. The yield of this alkylation was limited by the decomposition of intermediate **8** under these reaction conditions. Reductive alkylation of secondary amine **9** using propionaldehyde gave enone **11** in good yield and could be performed in the same pot following the previous reductive alkylation. However, to have better control over the double bond selectivity in the second reduction step, it was preferred to workup the reaction mixture after the first step.

Condensation of *N*-methyl-*N*-*n*-propylamine, *N*-ethyl-*N*-*n*-propylamine, or *N*-methyl-*N*-propargylamine with precursor **7** required heating in a sealed flask in the presence of powdered 4 Å molecular sieves. As reported in the synthesis of (−)-**6**, it was preferred to proceed with the reduction of the enamine without purification.[17,18] Yields were moderate since the selectivity for reduction of the desired double bond was difficult to control. Use of methanol or 1,2-dichloroethane as solvent increased reaction speed but decreased selectivity.[23,25] In tetrahydrofuran the selectivity of the reaction could be controlled by maintaining slightly acidic conditions at a low temperature. Although both primary and secondary amines react with **7** to give an enamine, reduction of the primary enamine proceeds most selective for the desired double bond.[26−28]

The 3,3-dimethyl analogue **16** was synthesized analogously to (−)-**6** (Scheme 3).[17] Dimedone (**15**) was reacted with paraformaldehyde and dipropylamine in hot toluene in the presence of powdered 4 Å molecular sieves followed by treatment with acetone. The presence of two methyl groups made the reaction proceed markedly slower than for 1,3-cyclohexadione used in the synthesis of **6**. After heating for 50 h, no further reaction was observed and the reaction was stopped. After workup, the enamine intermediate was reduced to give **16**.

Pharmacology

All new enones 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.[21] In this model, rats receive a unilateral lesion of the medial forebrain bundle that projects dopaminergic neurons to the stri-

Table 2. The Pharmacological Effect of (±)-**6** and Some of Its Analogs at Three Doses po in the Ungerstedt Rat Model for Parkinson's Disease[a]

	total full contralateral turns ($x \pm$ SEM)					
enone	0.1 mg kg^{-1}	n[b]	0.3 mg kg^{-1}	n	1.0 mg kg^{-1}	n
(±)-**6**	2312 ± 440	(10)	5354 ± 748	(8)	8787 ± 1450	(5)
(±)-**10**	-[c]	-	5194 ± 1543	(8)	7540 ± 1358	(8)
(±)-**11**	262 ± 75	(7)	-	-	503 ± 85[d]	(7)
(±)-**12**	2928 ± 961	(4)	5740 ± 491	(4)	-	-
(±)-**13**	4840 ± 757	(8)	8901 ± 1824	(8)	-	-
(±)-**14**	713 ± 237	(8)	513 ± 357	(8)	-	-
(±)-**16**	-	-	23 ± 12[d]	(4)	204 ± 179[d]	(4)

[a] Numbers noted are the cumulative full contralateral turns in 12 h. [b] n, number of rats tested. [c] Not tested. [d] 3 h totals.

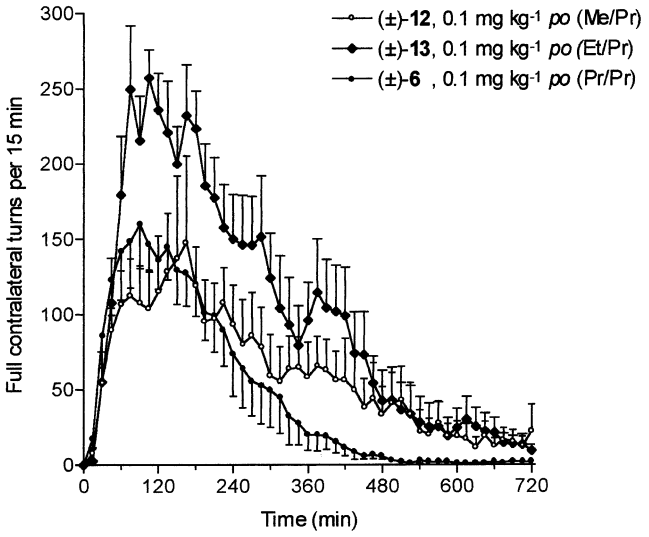


Figure 2. Pharmacological effect of 0.1 mg kg^{-1} po of (±)-**6** (n = 10), (±)-**12** (n = 4), and (±)-**13** (n = 8); in the Ungerstedt model for Parkinson's disease expressed as full contralateral rotations per 15 min or cumulative over 12 h. Each point is the mean ± SEM for n determinations.

atum. 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 enones tested.

Results and Discussion

The Ungerstedt Rat Rotation Model. In Table 2, the total cumulative full contralateral rotations of the new enones are presented with **6** as a reference compound. Enones **10**, **12**, and **13** induced strong effects after oral administration, at all doses. Both the *N*-(3-fluoro)-*N*-propyl- and the *N*-methyl-substituted compounds have a pharmacological effect similar to that of the reference compound. *N*-Ethyl-*N*-*n*-propyl-substituted enone **13** was the most potent compound of the series, inducing a significantly greater effect than **6** at 0.1 mg kg^{-1} po. Enones **11**, **14** and **16**, of which the latter cannot be transformed to the corresponding catecholamine, induced very weak or no significant effects.

Figure 2shows the pharmacological effects of enones **6**, **12,** and **13** at 0.1 mg kg^{-1} po over time. The three enones have similar rapid onset of action, inducing maximum effects after about 120 min after which the effects gradually wear off. Statistical analyses of the data show that the effects of enone **13** are significantly different from enone **6** ($p < 0.01$). Significant pharmacological effects were recorded for **6** (15−525 min), **12** (30−420 min), and **13** (30−720 min). A saline control curve was not included as it coincides with the *x*-axis.

The order of potencies observed for enones **12** (Me/n-Pr), **13** (Et/n-Pr), and **6** (n-Pr/n-Pr) at both 0.1 mg kg^{-1} po and at 0.3 mg kg^{-1} po is different than for the corresponding aminotetralins, which are the (anticipated) active metabolites. For aminotetralins, *N*,*N*-di-*n*-propyl substitution has been considered to be optimal for the pharmacological effect.[29] In fact, McDermed et al. report a 133-fold increased potency of (±)-**2** over its *N*-methyl-*N*-*n*-propyl analogue in inducing D_1/D_2 related motor behavior in the rat.[30] The mismatch in pharmacological activity of the enones and their corresponding catecholamines is currently being studied.

Brain Extraction Experiments. To gain further insight into the bioactivation mechanism of the enone prodrugs, rats were administered relatively high doses of **13** or (−)-**6** after which their brain was removed, homogenized, extracted, and analyzed by GC-MS to identify possible metabolites after administration. Vehicle only was administered to provide blank experiments. Standard solutions of **1**, **2**, (−)-**6**, and **13** were used to determine retention time and fragmentation pattern.

Figures 3 and 4 show the mass spectra and fragment assignment after GC-MS (EI^+) analyses of the brain extracts. The M^+ ion and fragments of **13** and (−)-**6** are shown in A and B, respectively; C and D show the mass spectra of two newly observed analytes. Both M^+ ions of C and D and the primary fragments (McLafferty rearrangement) have an increased mass of 16 amu with respect to the administered enones.[31] However, the fragments resulting from a retro-Diels−Alder reaction of the aminocyclohexene ring, as well as their relative intensity, remain the same (113 and 127) thereby ruling out a possible *N*-oxide and suggesting that metabolism took place on the enone ring. Further it is evident that the fragments of prodrugs and metabolites after loss of the *N*,*N*-dialkylamine moiety are different (147 vs 149). Interestingly, for the metabolites, instead of a fragment of 165 amu (149 + 16), a fragment 18 amu lighter was detected. These data suggest that the enone rings of **13** and (−)-**6** were hydroxylated in vivo and dehydrate upon fragmentation in the GC-MS. In fact, α′ and γ hydroxylations of enones such as testosterone and levonorgestrel are known metabolic pathways.[32−34] Since oxidation of an α′-hydroxy-enone can give a catechol, this metabolite may constitute an intermediate structure in the bioactivation of enones to their corresponding catechols.[35] Catecholic or phenolic aminotetralins were not detected under this protocol (limit of detection for **1** and **2** were 10^{-7} M and 10^{-8} M, respectively).

In conclusion, the pharmacological evaluation of a series of racemic analogues of (−)-**6** has shown dopamine agonist related pharmacological activity in vivo of most analogues. Enones **10**, **12**, and **13** have similar or increased potency over **6** in the Ungerstedt rat rotation model of Parkinson's disease. Since the pharmacological

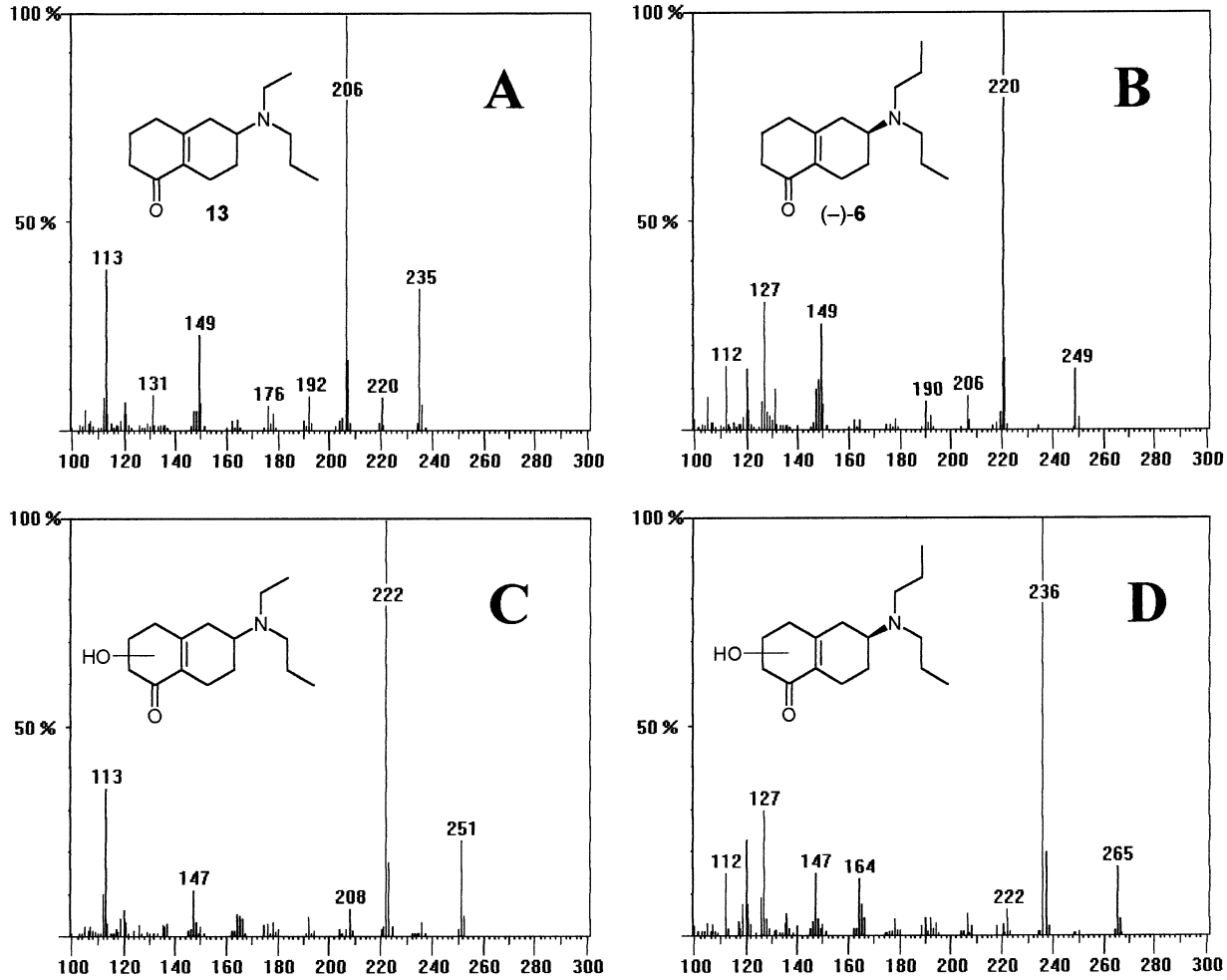


Figure 3. EI mass spectra (M^+) of (A) **13**, (B) (−)-**6**, (C) the observed metabolite of **13,** and (D) the observed metabolite of (−)-**6**.

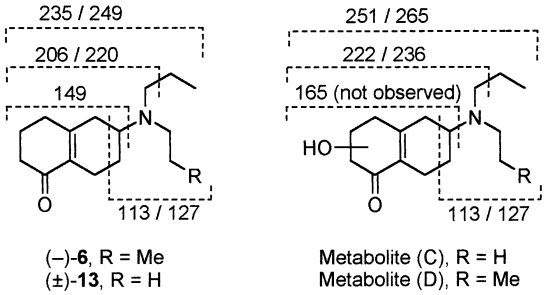


Figure 4. Some important ions observed in the fragmentation of (−)-**6**, **13**, and their metabolites.

effect of **6** and its fluorinated analogue (**10**) are similar, **10** may be of use in PET studies. The observation of similar metabolites of (−)-**6** and **13** indicates that both enones, at least partly, follow the same route of metabolism.

Experimental Section

Chemistry. 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 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 tetramethylsilane (TMS). Coupling constants are given in Hertz (Hz). The spectra recorded were consistent with the proposed structures. IR spectra were obtained on an 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.

6-*N*-(*n*-Propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (8). To a stirred solution of 3,4,7,8-tetrahydro-2*H*,5*H*-naphthalene-1,6-dione (0.50 g, 3.0 mmol)[22] in dry tetrahydrofuran (15 mL) were added *n*-propylamine (0.28 mL, 3.0 mmol) and $NaBH_3CN$ (0.29 g, 4.5 mmol). After stirring for 30 min, acetic acid (0.18 mL, 3.0 mmol) was added dropwise. Stirring was continued for an additional 3 h at room temperature, and then the solvent was evaporated. The residue was partitioned between diethyl ether (50 mL) and 50% aqueous Na_2CO_3 (25 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and evaporated to give 0.7 g of a colorless oil which was used without further purification. MS (EI) *m*/*z* 207 (M^+).

6-[*N*-(3-Fluoro-*n*-propyl)-*N*-*n*-propyl]amino-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (10). A mixture of **8** (0.7 g, ∼3.0 mmol), Cs_2CO_3 (2.7 g), 1-bromo-3-fluoropropane (1.22 g, 10.8 mmol) in acetonitrile (25 mL) was heated to 80 °C for 36 h in a sealed flask. After cooling, another portion of 1-bromo-3-fluoropropane (1.22 g, 10.8 mmol) was added and heating was continued for 8 h. The reaction mixture was then cooled to room temperature and diluted with ether (25 mL). Filtration and evaporation of the solvents gave 0.5 g of dark

oil which was purified by column chromatography (silica, dichloromethane/ethanol, 100:1). The product was converted to the hydrochloride salt, which was recrystallized from diethyl ether/acetone. Yield: 0.14 g, 0.5 mmol (15%), mp 135−139 °C. IR (KBr) 2946, 2452, 1660, 1387 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.59 (dt, 1H, J = 5.7 Hz), 4.35 (dt, 1H, J = 5.7 Hz), 2.71−2.77 (m, 1H), 2.12−2.58 (m, 10H), 1.61−2.05 (m, 8H), 1.18−1.48 (m, 3H), 0.82 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 198.7, 156.5, 131.7, 82.1 (d, 83.7, 80.4, CH_2F, J = 163.7 Hz), 55.4, 45.5, 45.4, 37.5, 34.3, 31.1, 29.7 (d, 29.8, 29.5, CH_2CH_2F, J = 19.4 Hz), 24.0, 22.7, 22.2, 21.7, 11.5 ppm; MS (EI) m/z 267 (M^+); Anal. ($C_{16}H_{26}FNO\cdot HCl$), C, H, and N.

6-[*N*-(2-(Thiophen-2-yl)ethyl)amino]-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (9). Preparation according to the method used for **8**, on the same scale using 2-thiophen-2-ylethylamine (0.35 mL, 3.0 mmol) yielding 0.83 g of a colorless oil which was used without further purification. ^1H NMR ($CDCl_3$) δ 7.14 (d, 1H), 6.93 (t, 1H), 6.82−6.92 (m, 1H) 2.91−3.10 (m, 4H), 2.75−2.87 (m, 1H), 2.34−2.55 (m, 4H), 1.87−2.28 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$) δ 198.7, 165.9, 154.5, 142.0, 131.7, 126.7, 125.0, 123.6, 52.2, 47.9, 38.3, 37.5, 31.0, 27.9, 22.1, 20.9 ppm.

6-[*N*-*n*-Propyl-*N*-(2-(thiophen-2-yl)ethyl)amino]-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (11). The oil was dissolved in methanol (60 mL), and propionaldehyde (3.0 mL, 45 mmol) was added. After stirring at room temperature for 30 min, $NaBH_3CN$ (0.30 g, 4.8 mmol) was added slowly and the mixture was stirred overnight. Stirring was continued for an additional 3 h at room temperature after which the solvent was evaporated. The residue was partitioned between diethyl ether (100 mL) and 10% aqueous $NaHCO_3$ (25 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (4 × 40 mL). The combined ethereal layers were dried ($MgSO_4$), filtered, and evaporated. The resulting colorless oil was purified by column chromatography (silica, dichloromethane/ethanol, 20:1) was converted to the hydrochloride salt, which was recrystallized from diethyl ether/acetone. Yield 0.61 g, 1.7 mmol (58%), mp 189−192 °C. IR (KBr) 2943, 2612, 1655, 1389, 850, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10 (d, 1H), 7.07 (t, 1H), 6.77−6.91 (m, 1H), 3.55−3.71 (m, 3H), 2.73−2.92 (m, 4H), 2.31−2.71 (m, 4H), 2.20 (br d, 2H), 1.87−2.22 (m, 3H), 1.28−1.56 (m, 5H), 0.86 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 198.7, 156.3, 141.9, 131.7, 126.4, 124.4, 123.1, 56.0, 52.4, 37.5, 34.4, 31.3, 31.2, 29.8, 24.4, 22.7, 22.1, 22.0, 11.6 ppm; MS (EI) m/z 317 (M^+); Anal. ($C_{19}H_{27}NOS\cdot HCl$) C, H, and N.

6-(*N*-Methyl-*N*-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (12). To a stirred solution of 3,4,7,8-tetrahydro-2*H*,5*H*-naphthalene-1,6-dione (0.25 g, 1.52 mmol)[22] and powdered 4 Å molecular sieves (1 g) in toluene (10 mL) was added *N*-methyl-*n*-propylamine (0.12 g, 1.54 mmol). The mixture was heated in a sealed flask to 60 °C for 18 h, and after cooling another portion of *N*-methyl-*n*-propylamine (0.12 g, 1.54 mmol) was added. Heating was then continued for 8 h. Workup consisted of cooling, filtration, rinsing the residue with ether (5 × 10 mL), and evaporation of the solvents. The resulting yellow/brown solid was dissolved in methanol (15 mL) and cooled to 0 °C, and the pH was adjusted to 4 by adding acetic acid. Then $NaBH_3CN$ (0.11 g, 1.65 mmol) was added slowly. After stirring at 0 °C for 30 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue partitioned between 50% aqueous $NaHCO_3$ (20 mL) and ether (50 mL). After separation of the layers, the aqueous layer was extracted with ether (3 × 25 mL). The combined ether layers were washed with brine, dried (Na_2SO_4), and evaporated. The resulting oil was purified by column chromatography (silica, dichloromethane/methanol, 20:1) and subsequently converted to the hydrochloride salt in 1 N HCl in diethyl ether, which was recrystallized from diethyl ether/acetone. Yield: 0.12 g, 0.45 mmol (30%), mp 140−143 °C. IR (KBr) 2937, 2451, 1652, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52−2.60 (m, 2H), 2.30−2.42 (m, 4H), 2.20−2.24 (m, 6H), 1.90−1.97 (m, 4H), 1.24−1.50 (m, 4H), 0.85 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 198.9, 156.1, 131.7, 58.1, 55.4, 37.5, 37.4, 33.7, 31.1, 24.2, 22.5, 22.1, 20.4, 11.6 ppm; MS (EI) m/z 221 (M^+); Anal. ($C_{14}H_{23}NO\cdot HCl$) C, H, and N.

6-(*N*-Ethyl-*N*-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (13). Preparation according to the method used for **12**, using **7** (0.75 g, 4.30 mmol)[22] and *N*-ethyl-*n*-propylamine (0.41 g, 4.70 mmol). Yield: 0.51 g, 1.87 mmol (48%), mp 157−158 °C. IR (KBr) 2944, 2446, 1652, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71−2.78 (m, 1H), 2.51 (q, 2H), 2.27−2.41 (m, 9H), 1.83−1.94 (m, 4H), 1.17−1.44 (m, 3H), 0.97 (t, 3H), 0.85 (t, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 198.6, 156.1, 131.7, 55.5, 51.5, 43.9, 37.5, 34.4, 31.2, 24.4, 22.6, 22.1, 21.6, 13.4, 11.5 ppm; MS (EI) m/z 235 (M^+); Anal. ($C_{15}H_{25}NO\cdot HCl$) C, H, and N.

6-(*N*-Methyl-*N*-propargylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (14). Preparation according to the method used for **12**, using **7** (0.25 g, 1.40 mmol)[22] and *N*-methylpropargylamine (0.13 mL, 1.54 mmol). Yield: 0.18 g, 0.71 mmol (51%), mp 120−123 °C. IR (KBr) 3188, 2931, 2467, 1666, 1389 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (d, 2H), 2.53−2.63 (m, 1H), 2.17−2.45 (m, 10H), 1.86−2.11 (m, 4H), 1.11−1.27 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 198.6, 154.8, 131.6, 73.1, 56.3, 42.9, 38.4, 37.4, 35.4, 31.0, 25.2, 22.1, 21.7 ppm; MS (EI) m/z 217 (M^+); Anal. ($C_{14}H_{19}NO\cdot HCl$) C, H, and N.

6-(*N*,*N*-Di-*n*-Propylamino)-3,3-dimethyl-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one (16). Dimedone (**15**) (5.0 g, 35.7 mmol), paraformaldehyde (1.1 g, 35.7 mmol), dipropylamine (3.8 g, 37.5 mmol), and powdered 4 Å molecular sieves (18 g) were mixed in toluene (55 mL). Under vigorous stirring the mixture was heated to 85 °C for 1 h. Acetone (2.71 mL, 37.1 mmol) was introduced and heating continued for 50 h. After cooling, the mixture was filtered and the residue was rinsed thoroughly (ethyl acetate). The organic layer was concentrated to about 50 mL and washed with 4 N HCl (5 × 50 mL). The combined acidic layers were basified to pH = 9 using 4 N NaOH and then extracted with ethyl acetate (5 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give a red solid (3.85 g, crude). The solid was dissolved in methanol (50 mL), and acetic acid (2.0 mL) was added. After cooling the mixture to 0 °C, $NaBH_3CN$ (0.90 g, 14.3 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature overnight. Workup consisted of evaporation of the solvent and partitioning of the residue between 50% aqueous $NaHCO_3$ (20 mL) and ether (50 mL). After separation of the layers, the aqueous layer was extracted with chloroform (3 × 25 mL). The combined ether layers were washed with brine, dried (Na_2SO_4), and evaporated. The resulting oil was purified by column chromatography (silica, dichloromethane/methanol, 20:1) and subsequently converted to the hydrochloride salt in 1 N HCl in diethyl ether, which was recrystallized from diethyl ether/acetone. Yield: 2.26 g, 7.2 mmol (21%), mp 98−102 °C. IR (KBr) 2965, 2425, 1655, 1393 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57−2.82 (m, 2H), 2.43 (t, 3H), 1.91−2.21 (m, 8H), 1.38−1.50 (m, 6H), 1.01 (s, 3H), 0.96 (s, 3H), 0.85 (t, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 198.9, 153.7, 130.5, 55.9, 52.3, 51.1, 45.3, 34.5, 32.9, 29.1, 27.0, 24.2, 22.4, 21.6, 11.6 ppm; MS (EI) m/z 277 (M^+); Anal. ($C_{18}H_{28}NO\cdot HCl\cdot 1/2H_2O$) C, H, and N.

Pharmacology. All enones were tested as hydrochloride salts unless noted otherwise. All in vivo experiments were performed at Pfizer Global Research & Development (Ann Arbor, MI). Brain extraction experiments were performed at the laboratory animal unit of the Rijksuniversiteit Groningen, The Netherlands.

The Ungerstedt Model for Parkinson's Disease. The contralateral turning experiments were conducted essentially according to the original reference by Ungerstedt and Arbuthnott.[21] Briefly, rats were lesioned in right medial forebrain bundle (P4.8 mm, L1.1 mm, V-8.2 mm from bregma) with 8 μg/4 μL of 6- hydroxydopamine HBr in saline with ascorbic acid 1 mg/mL added. After 3 weeks recovery, completeness of lesion was assessed with apomorphine 50 μg kg^{-1} sc. Only animals rotating more than 100 turns in 1 h were used in subsequent experiments. Rats were removed from home cages

in morning, weighed, dosed, and placed into harnesses in a rotorat apparatus. In the 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 are used once weekly.

Brain Extraction. The experiments were largely adapted from Feenstra et al.[36] Male Wistar rats were administered of 30 mg kg^{-1} *sc* of **13** or 10 mg kg^{-1} *sc* of (−)-**6**, or a saline solution. After 30 min, all prodrug treated animals showed stereotypic dopaminergic behavior. The rats were then stunned and decapitated, and the whole brain was removed quickly and kept in liquid N_2. Tissue homogenates were prepared with a Teflon pestle in 5 mL glass tubes filled with 0.5 mL of 0.1 M $HClO_4$ solution. The homogenates were poured into polypropylene tubes. The pestle and glass tubes were rinsed with 0.5 mL of 0.1 M $HClO_4$ solution that was added to the homogenate (total of about 3 mL). The homogenates were centrifuged at 3000 g at 4 °C for 15 min. The supernatants were completely decanted into glass tubes. The pH was adjusted to 11 by addition of saturated Na_2CO_3 (300 μL) solution. To the alkaline solution was added diethyl ether (3 mL), and this was shaken vigorously for 30 min. Tubes were then centrifuged at 3000*g* at 4 °C for 5 min, and 80% of the organic layer was removed with a pipet. The extraction procedure was repeated three times, and the organic layers were combined and evaporated under a stream of N_2 gas at room temperature. The residue was dissolved in toluene (150 μL). GC-MS analyses was performed by splitless injection of 4 μL of the solution into a Unicam 610-Automass 150 GC/MS system, fitted with an Alltech CpSil, 10 m column. Injection at 275 °C, column at 100−320°C, ramp rate 10 °C/min, EI mass detection. Standard solutions of **1**, **2**, **6**, and **13** were injected on the GC-MS system in the range of 10^{-10} M to 10^{-5} M to determine retention time and detection limit (10^{-7} M for **2**, others 10^{-8} M).

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