Substituted (S)-Phenylpiperidines and Rigid Congeners as Preferential Dopamine Autoreceptor Antagonists: Synthesis and Structure–Activity Relationships

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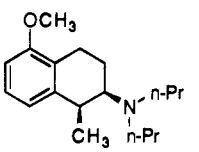
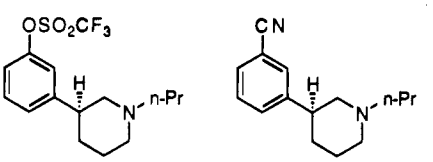
A series of (*S*)-phenylpiperidines in which the substituents on the aromatic ring and nitrogen have been varied has been prepared. They have been evaluated pharmacologically to explore the importance of these substituents for the interaction with central dopamine (DA) receptors. On the basis of biochemical and behavioral data in rats, several of these compounds are characterized as centrally acting DA autoreceptor antagonists. (*S*)-Phenylpiperidines having an aromatic substituent with a high group dipole moment in the 3-position, i.e., *meta* with respect to the piperidine ring, and being N-substituted with a propyl group were found to be highly active *in vivo* on the synthesis and turnover of dopamine. However, they do not induce strong hypoactivity or catalepsy. Interestingly, the most active compounds *in vivo* were found to display only low affinity for DA D_2 and D_3 receptors *in vitro*. In addition, 7-triflate-substituted octahydrobenzo[*f*]quinolines and 6-triflate-substituted hexahydro-1*H*-benz[*e*]indoles have been prepared and pharmacologically evaluated. The *trans* isomers of these rigid structures were found to display a pharmacological profile similar to that of the flexible phenylpiperidines. The corresponding *cis* isomers were found to be inactive *in vivo*.

Introduction

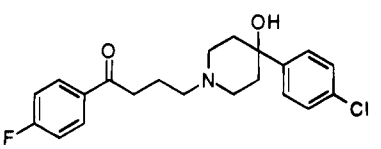
In the search for compounds with pharmacological profiles similar to compound **1a** (*cis*-(+)-5-methoxy-1-methyl-2-(di-*n*-propylamino)tetralin, *cis*-(+)-UH232),[1,2] we have found that compounds **6** and **10** with the *S*-configuration are structures with interesting pharmacodynamic and pharmacokinetic properties.[3] Like classical neuroleptics (e.g., haloperidol)[4] and "atypical antipsychotics" (e.g., remoxipride),[5] they increase the firing of dopamine (DA) neurons as well as the synthesis and turnover of dopamine but are not cataleptogenic in rodents.[6,7] Rather, compounds **6** and **10** act as mild behavioral stimulants. According to the prevailing hypothesis, the behavioral activation is thought to be caused by a preferential antagonism of nerve terminal DA autoreceptors leading to an increased synthesis and release of DA and subsequent increase in psychomotor activity. Still, **6** and **10** are able to antagonize the biochemical and behavioral effects of direct and indirect DA agonists such as apomorphine and *d*-amphetamine.[8] However, this new class of phenylpiperidines have relatively low affinity for D_2 receptors in *in vitro* binding assays.[3] It has been speculated that compounds of this structural class may be useful in the treatment of both positive and negative symptoms in schizophrenia[9,10] and possibly also for other indications such as depression and the pharmacological treatment of drug addiction.[11,12]



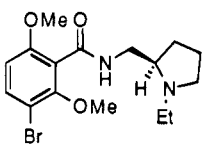
1 a



6 **10**



haloperidol



remoxipride

Compounds **6** and **10** emanate from the partial DA D_2 agonist **1b** ((−)-3-(3-hydroxyphenyl)-1-propylpiperidine, (−)-3-PPP, Preclamol)[13–15] and have some physicochemical properties in common. For compounds **6** and **10**, it has been suggested that a lack of hydrogen bond-donor properties on the aromatic ring (e.g., OH or an isosteric hydrogen-donating functionality such as an indole N-H[16]) is important to diminish the intrinsic activity at the autoreceptors.[3] Accordingly, removing the hydrogen bond-donating ability of **1b** by O-methy-

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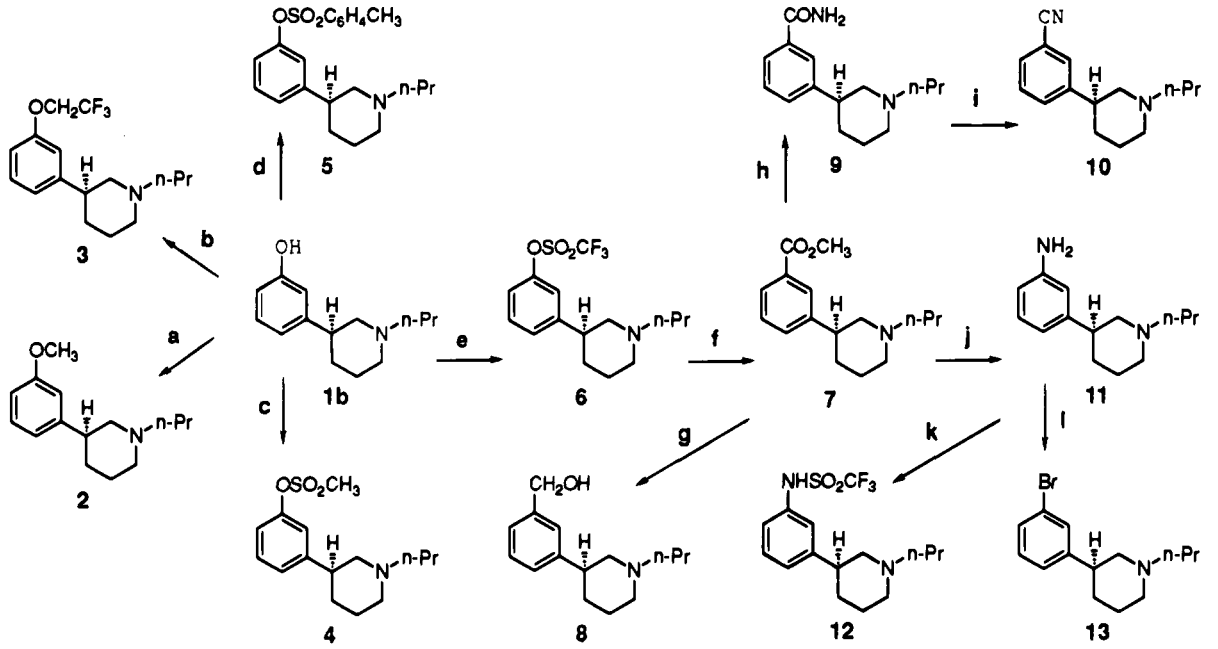
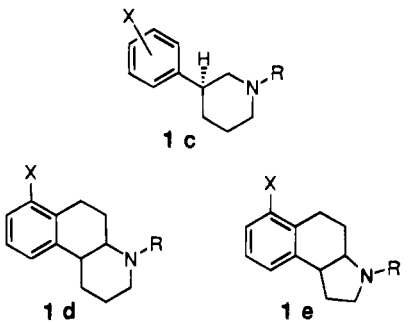
Scheme 1[a]



[a] Reagents and conditions: (a) NEt_3, NaOH, $(CH_3O)_2SO_2$, THF; (b) NaH, *p*-$TosOCH_2CF_3$, DMF, Δ; (c) NEt_3, CH_3SO_2Cl, CH_2Cl_2; (d) NEt_3, *p*-TosCl, CH_2Cl_2; (e) NEt_3, $(CF_3SO_2)_2O$, CH_2Cl_2; (f) $Pd(OAc)_2$/dppp, CO(g), NEt_3, MeOH, Δ; (g) $LiAlH_4$/diethyl ether; (h) MeONa/MeOH, $HCONH_2$, DMF, Δ; (i) $POCl_3$/DMF, Δ; (j) NaN_3, concentrated H_2SO_4, CH_2Cl_2, Δ; (k) NEt_3, $(CF_3SO_2)_2O$, CH_2Cl_2; (l) $NaNO_2$, CuBr, 48% HBr, Δ.

lation, yielding **2**, results in a compound with only weak agonist activity (reserpinized rats, Table 2). In addition, **2** displays only weak, if any, antagonist-like activity in nonpretreated habituated rats. This is in sharp contrast to the results obtained with compounds **6** and **10**, which are powerful antagonists at DA autoreceptors. The above results suggests that, apart from a lack of hydrogen-bonding properties, there are other structural requirements that are crucial for antagonist activity within this series of phenylpiperidines. Consequently, the importance of proper selection of the aromatic substituent, in order to yield antagonists in a series of aminotetralins, has recently been investigated.[17] Substitution of the methoxy group in **1a** for a triflate or a cyano group reduces the antagonist-like properties at the DA autoreceptors, shown by lower levels of released DA and metabolites than for **1a**. Thus, in contrast to the phenylpiperidines, strongly electron-donating groups (e.g., -OMe) seem to be important for the antagonistic properties at presynaptic autoreceptors of 5-substituted-1-methyl-2-aminotetralins **1a**.

To gain further insight about the physicochemical properties (lipophilic, electronic, and/or sterical) that are of importance for the DA receptor antagonistic properties of compounds **6** and **10**, we now report on the synthesis and biological activity of a series of compounds with the generic structure **1c**. All compounds have been evaluated *in vitro* in D_1, D_2, D_3, D_4, and 5-HT_{1A} binding assays in addition to assaying their biochemical and behavioral activity *in vivo*. The maximal change in tissue dihydroxyphenylalanine (DOPA accumulation) or dihydroxyphenylacetic acid (DOPAC levels) and dopamine release has been used to characterize their profile at the DA autoreceptors. Furthermore, to investigate if the aromatic substituent (e.g., OSO_2CF_3 and CN) has a different impact on the pharmacological profile in rigid as compared to flexible structures (**1c**), we have synthesized the conformationally restricted analogs **1d**,**e**. The *cis* and *trans* isomers of both generic structures have been evaluated. This evaluation may provide some information about the "antagonist conformation" of the flexible phenylpiperidine system.

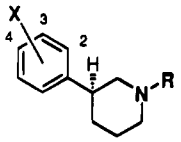


Chemistry

Compounds of the general formula **1c** were obtained *via* transformations of (−)-3-(3-hydroxyphenyl)-1-propylpiperidine (**1b**) or its substituted derivatives. The preparations of analogs bearing different substituents on the aromatic ring in position 3 are depicted in Schemes 1−3. Yields and analytical data are given in Table 1.

The methoxy derivative **2** was prepared from **1b** *via* triethylamine-catalyzed O-methylation with dimethyl sulfate in 88% yield.[18] The *O*-trifluoroethylated analog **3** was prepared in low yield by treating the sodium phenolate of **1b** with 2,2,2-trifluoroethyl *p*-toluenesulfonate in DMF. The sulfonate analogs **4**−**6** were prepared according to standard procedures.[19] The carboxy methyl ester **7** was prepared in high yields by palladium-catalyzed carbonylation of **6**.[20] A major side reaction in this step is a reductive elimination of the triflate group (10−15%) to yield **20**. This is a well-known problem in the palladium-catalyzed reactions. It

Table 1. Analytical and *in Vitro* Binding Data for D_2, D_3, and 5-HT_{1A} Receptors



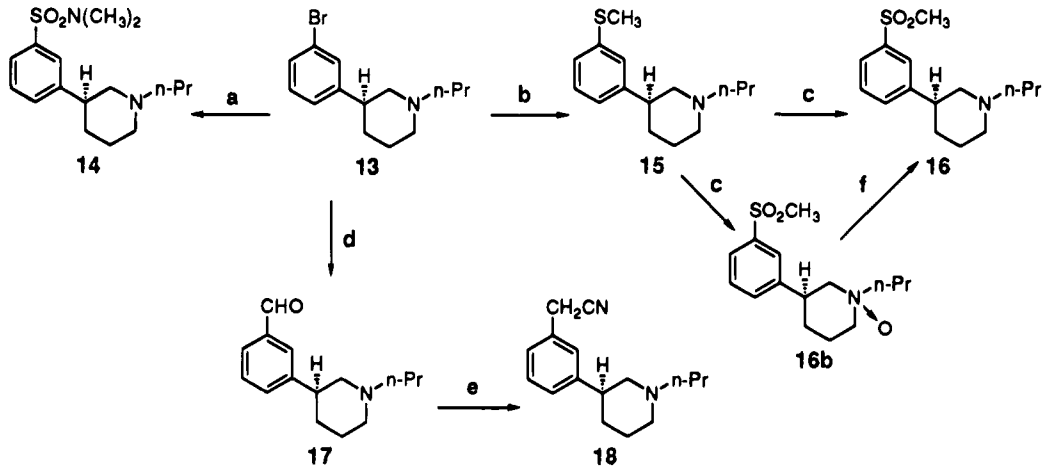
no.	X	R	% yield	formula[b]	K_i (nM)[a] D_2[c-e] [^{3}H]spiperone	D_2[f,g] [^{3}H]U-86170	D_3[f,g] [^{3}H]spiperone	5-HT_{1A}[c,h] [^{3}H]-8-OH-DPAT
1b	3-OH[i]	*n*-Pr			100[h]	8.5 ± 1.1	132 ± 16	8000
2	3-OMe	*n*-Pr	88	$C_{15}H_{23}NO$·HCl	3440 ± 515	602 ± 138	1328 ± 57	3600
3	3-OCH_2CF_3	*n*-Pr	31	$C_{16}H_{22}F_3NO$·HCl	1670[h]	820 ± 157	1414 ± 202	1200
4	3-OSO_2CH_3	*n*-Pr	88	$C_{15}H_{23}NO_3S$·$C_4H_4O_4$	4170[h]	192 ± 19	978 ± 34	1380 ± 44[d]
5	3-$OSO_2C_6H_4CH_3$	*n*-Pr	78	$C_{21}H_{27}NO_3S$·HCl	1320[h]	162 ± 18	92 ± 10	1600
6	3-OSO_2CF_3[i]	*n*-Pr	92	$C_{15}H_{20}NF_3O_3S$·HCl	408 ± 115	40 ± 2	68 ± 3	1530 ± 15[d]
7	3-CO_2CH_3	*n*-Pr	84	$C_{16}H_{23}NO_2$·HCl	2170[h]	>1852	>1285	1600
8	3-CH_2OH	*n*-Pr	83	$C_{15}H_{23}NO$·HCl	410[h]	240 ± 20	1461 ± 143	2410
9	3-$CONH_2$	*n*-Pr	84	$C_{15}H_{22}N_2O$·0.5H_2O	>15 000	>1852	>1285	5040
10	3-CN[i]	*n*-Pr	92	$C_{15}H_{20}N_2$·HCl	1140 ± 282	119 ± 33	249 ± 39	>10 000
11	3-NH_2	*n*-Pr	76	$C_{14}H_{22}N_2$[j]	2000[h]	NT[k]	NT	5360
12	3-$NHSO_2CF_3$	*n*-Pr	48	$C_{15}H_{21}F_3N_2O_2S$	NT	>2000	>2000	>10 000
13	3-Br	*n*-Pr	57	$C_{14}H_{20}NBr$·HCl	533 ± 128	106 ± 7	171 ± 8	800
14	3-$SO_2N(CH_3)_2$	*n*-Pr	38	$C_{16}H_{26}N_2O_2S$·$C_4H_4O_4$	3390[h]	227 ± 15	170 ± 4	8160
15	3-SCH_3	*n*-Pr	81	$C_{15}H_{23}NS$·$C_4H_4O_4$·0.25H_2O	849 ± 133	49 ± 4	139 ± 12	887
16	3-SO_2CH_3	*n*-Pr	52 + 41	$C_{15}H_{23}NO_2S$·HCl	6270 ± 580	447 ± 45	1305 ± 249	2590 ± 30[d]
17	3-CHO	*n*-Pr	75	$C_{15}H_{21}NO$·HCl[l]	1120[h]	20 ± 2	83 ± 5	8110
18	3-CH_2CN	*n*-Pr	50	$C_{16}H_{22}N_2$·$C_4H_4O_4$	1229 ± 11	69 ± 20	509 ± 30	3260
19	3-CCH	*n*-Pr	52	$C_{16}H_{21}N$·HCl	709 ± 41	334 ± 18	339 ± 24	310
20	3-H	*n*-Pr	71	$C_{14}H_{21}N$·HCl	1490 ± 86	222 ± 18	777 ± 39	2050
21	3-CH_3	*n*-Pr	58	$C_{15}H_{23}N$·HCl	930[h]	430 ± 45	573 ± 37	1200
22	3-(3-thienyl)	*n*-Pr	70	$C_{18}H_{23}NS$·HCl·0.5H_2O	760 ± 38	134 ± 22	78 ± 6	160
23	3-$COCH_3$	*n*-Pr	74	$C_{16}H_{23}NO$·HCl	6540 ± 3460	>1852	2150 ± 132	4170
25	3-$CH_2CH_2CH_3$	*n*-Pr	88	$C_{17}H_{27}N$·HCl	392[h]	57 ± 6	86 ± 10	135
26	3-CN	H	84	$C_{12}H_{14}N_2$·$C_4H_4O_4$	2670[h]	314 ± 47	631 ± 45	8000
27	3-CN	Me	89	$C_{13}H_{16}N_2$·HCl[m]	8330[h]	1040 ± 159	1759 ± 92	>10 000
28	3-CN	Et	91	$C_{14}H_{18}N_2$·HCl	2330[h]	235 ± 21	514 ± 21	>10 000
29	3-CN	*i*-Pr	93	$C_{15}H_{20}N_2$·HCl	717[h]	106 ± 9	268 ± 37	>10 000
30	3-CN	allyl	64	$C_{15}H_{18}N_2$·HCl	1890 ± 263	254 ± 38	658 ± 48	9600
31	3-CN	propargyl	69	$C_{15}H_{16}N_2$·HCl	>15 000	1178 ± 257	>1362	>10 000
32	3-CN	*n*-Bu	76	$C_{16}H_{22}N_2$·$C_4H_4O_4$·0.25H_2O	617[h]	NT	NT	4480
33	3-CN	*s*-Bu	77	$C_{16}H_{22}N_2$·$C_4H_4O_4$	1050[h]	187 ± 26	105 ± 46	8070
34	3-CN	cpm[n]	80	$C_{16}H_{20}N_2$·$C_4H_4O_4$	3100 ± 354	519 ± 77	522 ± 35	6320
35	3-CN	pheet[o]	81	$C_{20}H_{22}N_2$·$C_4H_4O_4$	105[h]	22 ± 3	59 ± 4	120
36	3-CN	pheprop[p]	72	$C_{21}H_{24}N_2$·$C_4H_4O_4$	80[h]	29 ± 4	36 ± 2	180
37	3-CN	thiopheneet[q]	60	$C_{18}H_{20}N_2S$·$C_4H_4O_4$	102 ± 27	11 ± 1	56 ± 5	320
38	3-CN	$(CH_2)_3N(CH_3)_2$	38	$C_{17}H_{25}N_3$·2HCl·0.5H_2O[r]	2330[h]	NT	NT	7120
39	3-OSO_2CF_3	Me	91	$C_{13}H_{16}F_3NO_3S$[s]	11 800[h]	NT	NT	2240
40	3-OSO_2CF_3	Et	88	$C_{14}H_{18}F_3NO_3S$·HCl	1180[h]	NT	NT	1040
41	3-OSO_2CF_3	pheet	84	$C_{20}H_{22}F_3NO_3S$·$C_4H_4O_4$	40[h]	11 ± 1	19 ± 3	NT
42	2-OSO_2CF_3[t]	*n*-Pr	85	$C_{15}H_{20}F_3NO_3S$·HCl	92[h]	315 ± 21	3113 ± 235	1840
43	4-OSO_2CF_3[t]	*n*-Pr	92	$C_{15}H_{20}F_3NO_3S$·HCl	11 800[h]	1736 ± 239	1136 ± 62	>10 000
44	3,4-di-OSO_2CF_3	*n*-Pr	80	$C_{16}H_{19}F_6NO_6S_2$·HCl	6250[h]	1100 ± 99	338 ± 53	>10 000

[a] K_i values for displacement of the dopamine D_2 receptor antagonist spiperone, the dopamine D_2 receptor agonist U-86170, the dopamine D_3 receptor antagonist spiperone, or the 5-HT_{1A} receptor agonist 8-OH-DPAT. [b] Analyses for C, H, and N were within ± 0.4%. [c] Data from rat striatal membrane. [d] Values were obtained with six drug concentrations (10^{-4}–10^{-9} M) in which each value was determined in triplicate. [e] In addition, all compounds were also screened in D_2 cloned mammalian receptors expressed in CHO-K1 cells using [^{3}H]spiperone as ligand. All compounds display K_i > 217 except for compounds **1b** (K_i = 39 ± 7), **6** (48 ± 8), **10** (265 ± 54), **13** (170 ± 23), 14 (91 ± 8), **17** (145 ± 20), **33** (98 ± 10), **36** (60 ± 8), **37** (134 ± 8), and 41 (73 ± 5). [f] Data from cloned mammalian receptors expressed in CHO-K1 cells. [g] Values were obtained with 11 drug concentrations in which each value was determined in duplicate. [h] Values were obtained with six drug concentrations (10^{-4}–10^{-9} M) in which each value was determined from a single experiment. [i] Data taken from ref 3. [j] High-resolution mass spectrum calcd for $C_{14}H_{22}N_2$ (M^+): 218.1782. Found: 218.1770. [k] NT means not tested. [l] Anal. Calcd: C, 67.3. Found: C, 66.6. [m] Anal. Calcd: C, 66.0. Found: C, 65.4. [n] cpm: cyclopropylmethyl. [o] pheet: 2-phenylethyl. [p] pheprop: 3-phenylpropyl. [q] thiopheneet: 3-(2-ethyl)thiophene. [r] Anal. Calcd: H, 6.9; found: H, 7.9. [s] High-resolution mass spectrum calcd for $C_{13}H_{16}F_3NO_3S$ (M^+): 323.0803. Found: 323.0804. [t] Racemate.

has been suggested that the hydride source may be triethylamine.[21,22] An alternative approach to avoid this side reaction is the use of diisopropylethylamine as a base.[21] However, when we used diisopropylethylamine, the amount of reduced triflate increased to 40–45%. Analysis of another side product from this reaction, by ^{1}H-NMR and GC-MS, revealed that the piperidine ring of the starting material probably acted as the hydride source.

The hydroxymethyl analog **8** was obtained from methyl ester **7** through reduction with lithum alumium hydride ($LiAlH_4$). The carboxamide **9** was obtained *via* an efficient one-step synthesis from the ester **7** using a formamide–sodium methoxide reagent in dimethylformamide (DMF).[23] The primary carboxamide **9** was then dehydrated with phosphorus oxychloride in dry DMF to yield the corresponding cyano analog **10**.[24] The preparation of this compound has been reported earlier[3] in a one-step procedure starting with the triflate analog **6** *via* a palladium-mediated insertion of the cyanide group (52% yield). The overall yield of **10**, based on **6**, reported by us is 65–70%.

Scheme 2[a]



[a] Reagents and conditions: (a) i, *s*-BuLi/THF, SO_2(g), ii, $SOCl_2$, 40% $HNMe_2$, CH_2Cl_2; (b) *t*-BuLi/diethyl ether, CH_3SSCH_3; (c) *m*-CPBA, CF_3COOH; (d) *t*-BuLi/diethyl ether, DMF; (e) *t*-BuOK/1,2-DME, TOSMIC; (f) $TiCl_4$/NaI, CH_3CN.

Further transformation of the ester **7**, illustrated in Scheme 1, includes a Curtius rearrangement yielding the aniline **11**, using excess of sodium azide in a concentrated sulfuric acid–dichloromethane mixture.[25] Treatment of compound **11** with trifluoromethanesulfonic anhydride afforded **12** in a modest yield (48%). Compound **13** was prepared from **11** *via* the Sandmeyer reaction using cuprous bromide (57%).[26]

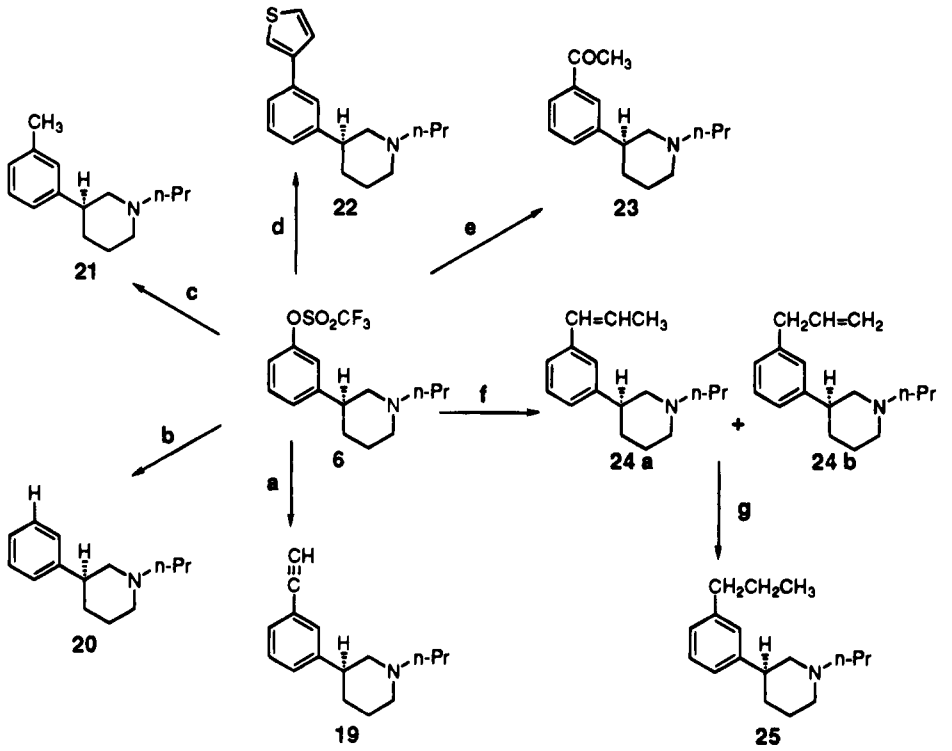
Scheme 2 shows the conditions used for the preparation of compounds **14**–**18**. Metal–halogen exchange[27] of the bromo intermediate **13** with *sec*- or *tert*-butyllithium and subsequent treatment of the reaction mixture with dimethyl disulfide or DMF afforded the methyl sulfide analog **15** (81%) or the formyl analog **17** (75%), respectively. The yields were significantly improved if the bromo analog **13** was distilled prior to use. Oxidation of compound **15** with 2.3 equiv of *m*-chloroperoxybenzoic acid in concentrated trifluoroacetic acid afforded compound **16** in a surprisingly low yield. According to GC-MS, no starting material or sulfoxide intermediate was detectable, but after extractive workup of the reaction mixture, only 60–70% of the organic material was recovered. A chromatographic separation of the crude material afforded a 50% yield of the pure product. The aqueous phase from the extractive workup was concentrated and the residue redissolved in absolute ethanol. Analysis of the ethanolic solution by means of TLC showed a product more polar than the sulfonyl analog **16**. The ^{1}H-NMR signals of the methylene groups around the nitrogen were shifted downward and broadened compared to those of **16**. We presume this impurity may be the *N*-oxide **16b**, although the reaction was performed in trifluoroacetic acid to protect the amino group. A survey of the literature reveals that many methods have been reported for the reduction of amine *N*-oxides. We found that **16** could be obtained from **16b** after a mild reduction using titanium tetrachloride/sodium iodide ($TiCl_4$/NaI) in acetonitrile.[28] With this extra procedure, the combined yield of compound **16** was enhanced to 93% after the chromatographic separation.

To prepare the sulfonamide **14**, the metalated compound **13** was treated with sulfur dioxide (gas), affording the corresponding lithium sulfinate which was then further treated with thionyl chloride. Subsequent treatment with a water solution of dimethylamine (40%) yielded the sulfonamide **14** (38%). Finally, the methylene cyano **18** can be prepared either from aldehyde **17**, *via* a "reductive" cyanation procedure using tosylmethyl isocyanide[29]/potassium *tert*-butylate in dry dimethoxyethane, or from alcohol **8**, which was chlorinated with thionyl chloride in methylene chloride followed by treatment with potassium cyanide in ethanol, in acceptable yield (unpublished data).

For the synthesis of the novel analogs **19**–**25**, we utilized an efficient palladium-catalyzed transformation of triflate derivative **6** (Scheme 3). Introduction of a ethynyl (**19**, 52%), methyl (**21**, 58%), or 3-thienyl group (**22**, 70%) was accomplished by palladium-catalyzed cross-coupling with the corresponding organostannanes, now commonly referred to as the Stille reaction.[30] Several attempts were made to obtain the allyl analog **24b** from allyltributyltin. Only mixtures of isomers, **24a,b** (the major product, **24a**, being the result of double-bond migration into conjugation with the ring),[31] were obtained in modest yield. Chromatographic separation of these isomers was unsuccessful. Therefore the mixture was hydrogenated to yield the propyl analog **25** using Pd/C and ammonium formate in refluxing methanol.[32] The triflate substituent was conveniently removed by treatment with formic acid in the presence of a palladium(II) acetate, affording compound **20** in high yield.[33] The acetyl group was introduced by a Heck coupling of **6** with butyl vinyl ether and subsequent hydrolysis with HCl solution to yield **23**.[34]

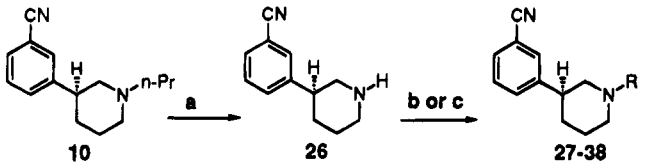
As shown in Scheme 4, compound **26** is the key intermediate in the synthesis of analogs **27**–**38**. The first attempt to obtain **26** from **10** using the von Braun reaction with cyanogen bromide failed.[35] Only traces of the desired product were obtained. Selective N-dealkylation of tertiary amines using alkyl or vinyl chloroformates is probably not feasible since the nitrile is quite sensitive to both acidic and basic conditions which are required to hydrolyze the initially formed carbamate.[36] A recently reported reagent for selective N-dealkylation utilizes α-chloroethyl chloroformate (ACE-Cl).[37] The advantage of the ACE-Cl reagent compared to other chloroformates is that it only requires refluxing methanol to cleave the initially formed carbamate. Treating compound **10** with excess of ACE-Cl in refluxing 1,2-dichloroethane and then in boiling methanol gave **26** in 84% yield.

Scheme 3[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, *n*-Bu_3SnCCH, LiCl, NEt_3, 1,4-dioxan, Δ; (b) $Pd(OAc)_2/PPh_3$, NEt_3, HCOOH, DMF, Δ; (c) $Pd(PPh_3)_4$, Me_4Sn, LiCl, NEt_3, 1,4-dioxan, Δ; (d) $Pd(PPh_3)_4$, *n*-Bu_3Sn-3-thienyl, LiCl, NEt_3, 1,4-dioxan, Δ; (e) i, butyl vinyl ether, $Pd(OAc)_2$/dppp, NEt_3, DMF, Δ, ii, 5% HCl; (f) $(PPh_3)_2PdCl_2/PPh_3$, *n*-$Bu_3SnCH_2CH{=}CH_2$, LiCl, NEt_3, DMF, Δ; (g) $HCONH_4$, Pd/C, MeOH, Δ.

Scheme 4[a]

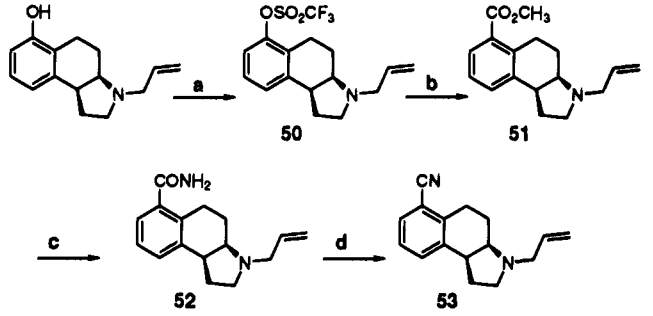


[a] Reagents and conditions: (a) i, $ClCO_2CH(Cl)CH_3$, 1,2-dichloroethane, Δ, ii, MeOH, Δ; (b) RCHO, $NaBH(OAc)_3$, CH_3COOH, 1,2-dichloroethane; (c) K_2CO_3, R-X, CH_3CN.

Compounds **27**–**28** were obtained from **26** *via* reductive amination of the corresponding aldehydes, using sodium triacetoxyborohydride as the reducing agent.[38] The remaining tertiary amines (**29**–**38**) were prepared from the secondary amine **26** by alkylation with the corresponding alkyl halide (I and Br, etc.) using ground potassium carbonate as the base and acetonitrile as the solvent. The triflates **39**–**50** were prepared from the corresponding known phenols by using a standard method.[3]

Scheme 5 shows the synthesis of a few 6-substituted *cis*- and *trans*-hexahydro-1*H*-benz[*e*]indoles. The triflate **50** was prepared from corresponding hydroxy analog.[39] The triflate was converted to methyl ester **51** in a manner similar to the preparation of **7** (Scheme 1). The carboxamide **52** was obtained *via* hydrolysis of **51** to the carboxylic acid followed by coupling with ammonia (gas) in the presence of diethyl cyanophosphonate (DEPC). The carboxamide **52** was then converted to the nitrile **53** *via* a preparation similar to that of the nitrile **10** (Scheme 1). In the *cis* series, the enantiomers were prepared, whereas the *trans* analogs were tested as the racemates.

Scheme 5[a]



[a] Reagents and conditions: (a) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (b) $Pd(OAc)_2$/dppp, CO(g), NEt_3, MeOH, Δ; (c) i, NaOH, MeOH/H_2O, ii, NH_3, DEPC, NEt_3/DMF; (d) $POCl_3$, DMF, Δ.

Pharmacology

The compounds were tested for their *in vitro* binding affinity (Tables 1 and 4) to rat striatal DA D_1 receptors (utilizing [^{3}H]SCH23390 as ligand), DA D_2 receptors (utilizing [^{3}H]spiperone as ligand), and cloned mammalian DA receptors expressed in CHO-K1 cells (using [^{3}H]U-86170 and [^{3}H]spiperone for D_2 DA receptors and [^{3}H]spiperone for D_3 and D_4 DA receptors). All compounds tested displayed less than 50% inhibition at 1 μM for D_1 and D_4 DA receptors. They were also tested for their affinity at 5-HT_{1A} receptors using [^{3}H]-8-OH-DPAT in either homogenized rat brain tissue or cloned CHO cells. To further establish the pharmacological profile of the compounds, attempting to gain information of their possible target(s) molecules in the CNS, we tested the compounds in an extended battery of CNS *in vitro* radioligand receptor binding assays according to standard methodology. All compounds tested displayed less than 50% inhibition at **1** μM for α_1- ([^{3}H]-prazosin), α_2- ([^{3}H]clonidine), and β-adrenoreceptor

Table 2. Effects on *in Vivo* DA Biochemistry (Striatum) and Locomotor Activity

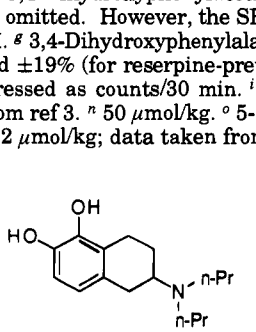
			nonpretreated habituated rats,[a] 100 μmol/kg sc		nonhabituated rats,[b] 100 μmol/kg sc		reserpine-pretreated rats,[c] 100 μmol/kg sc		brain dialysis,[d] 200 μmol/kg sc
no.	X	R	DOPAC[e]	LMA[f]	DOPA acc[g]	LMA[f]	DOPA acc[g]	LMA[h]	DA release
1b	3-OH	*n*-Pr	203*[i]	119 ± 12	141[j]	40[j]	25[j]	12 ± 2[j]	190*
2	3-OMe	*n*-Pr	149*	463 ± 28*	131*	160 ± 14*	66*	23 ± 9	NT[k]
3	3-OCH_2CF_3	*n*-Pr	NT	NT	96	90 ± 17	NT	NT	NT
4	3-OSO_2CH_3	*n*-Pr	276*	576 ± 72*	249*	154 ± 38	74*[l]	18 ± 6	234*
5	3-$OSO_2C_6H_4CH_3$	*n*-Pr	89	152 ± 62	NT	NT	NT	NT	NT
6	3-OSO_2CF_3	*n*-Pr	217*	290 ± 85*	264[m]	129[m]	89[m]	26[m]	223*
7	3-CO_2CH_3	*n*-Pr	140	297 ± 84*	NT	NT	NT	NT	NT
8	3-CH_2OH	*n*-Pr	138*	187 ± 28	118	123 ± 17	50*	3 ± 1	175*
9	3-$CONH_2$	*n*-Pr	114	203 ± 40	NT	NT	97[n]	NT	NT
10	3-CN	*n*-Pr	362*	653 ± 41*	268[m]	165[m]	105[m]	12[m]	252*
11	3-NH_2	*n*-Pr	NT	NT	128*	113 ± 17	91[n]	72 ± 38[n]	NT
12	3-$NHSO_2CF_3$	*n*-Pr	91	305 ± 66*	NT	NT	NT	NT	NT
13	3-Br	*n*-Pr	145*	470 ± 90*	199*	140 ± 6	101	15 ± 9	363*
14	3-$SO_2N(CH_3)_2$	*n*-Pr	355*	548 ± 23*	NT	NT	NT	NT	220*[n]
15	3-SCH_3	*n*-Pr	118*	313 ± 55*	NT	NT	92[n]	5 ± 2[n]	NT
16	3-SO_2CH_3	*n*-Pr	250*	368 ± 43*	319*	135 ± 17	95	10 ± 7	293*
17	3-CHO	*n*-Pr	127*	208 ± 51	NT	NT	92	5 ± 3	NT
18	3-CH_2CN	*n*-Pr	302*	887 ± 102*	207*	147 ± 36	57*	16 ± 5	NT
19	3-CCH	*n*-Pr	138	671 ± 137*	136*	237 ± 16*	NT	NT	265*
20	3-H	*n*-Pr	188*	353 ± 66	140*	126 ± 17	65*[n]	3 ± 1	473*
22	3-(3-thienyl)	*n*-Pr	88	229 ± 67	NT	NT	NT	NT	106[n]
23	3-$COCH_3$	*n*-Pr	183*	824 ± 107*	243*	139 ± 15	73*	7 ± 1	179*
25	3-$CH_2CH_2CH_3$	*n*-Pr	181*	734 ± 191*	190*[o]	205 ± 20*	62*[p]	11 ± 1	NT
26	3-CN	H	167*	575 ± 107	271*	193 ± 20*	NT	NT	NT
27	3-CN	Me	174*	277 ± 68*	215*	79 ± 2*	NT	NT	NT
28	3-CN	Et	264*	351 ± 59*	318*	113 ± 7	NT	NT	212*
29	3-CN	*i*-Pr	335*	366 ± 33*	301*	102 ± 15	NT	NT	NT
30	3-CN	allyl	298*	679 ± 190*	257*	143 ± 17*	85	3 ± 1	522*
31	3-CN	propargyl	146*	297 ± 51*	NT	NT	NT	NT	NT
32	3-CN	*n*-Bu	257*	1382 ± 190*	NT	NT	71*[n]	12 ± 3	NT
33	3-CN	*s*-Bu	267*	346 ± 52*	NT	NT	NT	NT	256*
34	3-CN	cpm	272*	518 ± 153*	285*	191 ± 31*	NT	NT	NT
35	3-CN	pheet	231*	510 ± 69*	176*	120 ± 36	NT	NT	NT
36	3-CN	pheprop	280*	484 ± 111*	NT	NT	NT	NT	NT
37	3-CN	thiopheneet	200*	500 ± 92*	NT	NT	NT	NT	NT
40	3-OSO_2CF_3	Et	300*	345 ± 44*	286*	103 ± 19	NT	NT	120
41	3-OSO_2CF_3	pheet	NT	NT	111[l]	144 ± 23[l]	66*	20 ± 20	89
42	2-OSO_2CF_3	*n*-Pr	83	621 ± 156*	102	101 ± 14	NT	NT	NT
43	4-OSO_2CF_3	*n*-Pr	85[q]	495*	NT	NT	NT	NT	NT
44	3,4-di-OSO_2CF_3	*n*-Pr	96	36	NT	NT	NT	NT	NT
(*R*)-apomorphine			65*[r]	491 ± 61*[l]	53*[s]	277 ± 14*[t]	20[t]	366 ± 36[t]	37*[u]
haloperidol			404*[v]	61 ± 20[v]	356*[x]	2 ± 1*[x]	NT	NT	211*[y]
remoxipride			313*	222	411*[n]	60 ± 26[n]	104[n]	5 ± 1	NT

[a] The animals were put into the activity meters and 60 min later injected sc with drug. The activity was measured for the subsequent 60 min. [b] Animals were injected with test drug 65 min and with NSD 1015 (100 mg/kg sc) 30 min before death. Controls received corresponding saline injections. Values are expressed as percent of saline controls. [c] Animals were injected with reserpine (5 mg/kg ip) 18 h, test drug 60 min, and NSD 1015 (100 mg/kg sc) 30 min before death. Controls received corresponding vehicle injections. Values are expressed as percent of saline controls. [d] Effects of tested compounds (60 min after administration) on DA release in the brain dialysis model after 200 μmol/kg sc (striatum). Values are expressed as percent of saline controls. [e] 3,4-Dihydroxyphenylacetic acid levels in rat striatum. Values are expressed as percent of saline controls. For clarity, SEM values were omitted. However, the SEM never exceeded ±22%. [f] Locomotor activity. Values are expressed as percent of saline controls; means ± SEM. [g] 3,4-Dihydroxyphenylalanine accumulation in rat striatum. For clarity, SEM values were omitted. However, the SEM never exceeded ±19% (for reserpine-pretreated rats, 12%). Values are expressed as percent of saline controls. [h] Locomotor activity. Values are expressed as counts/30 min. [i] *$p < 0.01$ or less. [j] Data taken from ref 15; 213 μmol/kg. [k] NT means not tested. [l] 25 μmol/kg. [m] Data taken from ref 3. [n] 50 μmol/kg. [o] 5-HTP (limb) = 52 ± 4*. [p] 5-HTP (limb) = 58 ± 3*. [q] HVA (limb) = 147 ± 20*. [r] 0.79 μmol/kg. [s] 0.64 μmol/kg. [t] 3.2 μmol/kg; data taken from ref 2. [u] 1.6 μmol/kg. [v] 0.8 μmol/kg. [x] 1.3 μmol/kg. [y] 5.3 μmol/kg.

([^{3}H]dihydroalprenolol)-, 5-HT_{1D} (α + β, cloned cells, [^{3}H]-5-OH-tryptamin)-,[40] 5-HT_2 ([^{3}H]ketanserin)-, acetylcholine muscarinic ([^{3}H]oxotremorine)-, benzodiazepine ([^{3}H]flunitrazepam)-, and opiate ([^{3}H]etorphine)-labeled sites.

In addition, the compounds were tested for their ability to displace the DA receptor agonist 5,6-dihydroxy-2-(di-*n*-propylamino)tetralin (Di-Pr-5,6-ADTN) from rat striatal binding sites *in vivo* and their concomitant ability to antagonize the locomotor hyperactivity induced by Di-Pr-5,6-ADTN (Table 3).[41-43]

In parallel to the *in vitro* screening, the compounds were tested for central DA and 5-HT receptor agonist and/or antagonist activity *in vivo* by the use of biochemical and behavioral methods.[1,15,44-49] The compounds were biochemically investigated for their ability to



Di-Pr-5,6-ADTN

control the synthesis, release, and metabolism of monoamines (DA, 5-HT, and NA) in reserpine-pretreated or nonpretreated rats, with or without habituation to their environment prior to drug treatment (Tables 2 and 5). The behavioral effects of the compounds tested were also monitored in these experiments. The concept of these biochemical and behavioral screening methods has been described earlier.[49] Furthermore we employed brain microdialysis to moni-

Table 3. Interactions with Di-Pr-5,6-ADTN *in Vivo*

compd	Di-Pr-5,6-ADTN displacement[a]	locomotor activity, % of ctrl[b]
4	55 ± 2** [c](100)[d]	46 ± 19*
6	54 ± 3**(100)	78 ± 36
10	66 ± 6**(100)[e]	31 ± 9**
16	45 ± 8**(100)	101 ± 17
20	20 ± 8(100)	90 ± 21
23	44 ± 6**(100)	81 ± 6
30	59 ± 4**(200)	46 ± 13*
33	59 ± 4**(200)	56 ± 15*
37	22 ± 5*(100)	61 ± 7*
remoxipride	48 ± 6*(100)[e]	91 ± 9
haloperidol	82 ± 6**(1.3)[e]	7 ± 1**
Di-Pr-5,6-ADTN	0(0.25)	100

[a] The animals were injected with Di-Pr-5,6-ADTN (0.25 μmol/kg sc) 100 min and the test compounds 40 min before death. Shown is the striatal level of Di-Pr-5,6-ADTN (after subtraction of cerebellum levels) expressed as percent of Di-Pr-5,6-ADTN controls. [b] The locomotor activity was recorded 5–35 min after injection of the test compounds and is expressed as percent of Di-Pr-5,6-ADTN controls (saline, 4412 ± 1322 counts/30 min; Di-Pr-5,6-ADTN, 9054 ± 546 counts/30 min). [c] *$P < 0.05$, **$P < 0.01$ or less. [d] dose μmol/kg. [e] Data taken from ref 57.

tor presynaptic effects on dopamine release of the tested compounds.[50] The data from experiments with haloperidol, remoxipride, *cis*-(+)-5-methoxy-1-methyl-2-(*n*-propylamino)tetralin (**57**), and the DA agonist apomorphine are included for comparison.

Results and Discussion

DA Agonist Properties of Substituted Phenylpiperidines. Hacksell et al.[51] reported on a series of racemic phenylpiperidines with different substituents on the aromatic ring. All compounds except the hydroxy substituted (i.e., racemic **1b**) were devoid of intrinsic activity (IA) at DA receptors in reserpine-pretreated rats. This assay is a model for the detection of agonist activity *in vivo*. Phenolic compounds with *R*-configuration in the *N*-alkyl-3-(3-hydroxyphenyl)piperidine series behave as DA receptor agonists with affinity and IA at both pre- and postsynaptic receptors.[52] The same bifunctional profile has been shown for the *S* enantiomers with N-substituents bulkier than *n*-propyl. Likewise, the *S* enantiomers with ethyl or *n*-propyl N-substituents seem to interact with both pre- and postsynaptic receptors. However, they have IA at presynaptic receptors but appear to possess antagonist-like properties at postsynaptic receptors.[52] More recently, developments in the area of molecular biology of DA receptors have led to the suggestion that the difference between DA autoreceptors and postsynaptic receptors is one of sensitivity rather than one of structural diversity.[53] This sensitivity difference is suggested to be due to greater DA receptor reserve at presynaptic versus postsynaptic sites.[54] Thus, a compound with a certain level of IA may have the ability to stimulate presynaptic DA receptors and at the same time display weak antagonistic properties at the postsynaptic receptors. Following this reasoning, compounds with higher IA may show up as postsynaptic DA D_2 agonists.

In vitro binding data on phenylpiperidines with the *S*-configuration (**1**–**44**, Table 1) show that they possess various affinities at the DA receptor sites defined by the dopamine agonist [^{3}H]U-86170 or the dopamine antagonist [^{3}H]spiperone. The affinities for these compounds are generally higher at the high-affinity agonist (HiAg) binding site (defined by [^{3}H]U-86170) at both rat striatal DA receptors and cloned mammalian DA D_2 and D_3 receptors than at the antagonist site, i.e., low-affinity agonist (LowAg) binding site (defined by [^{3}H]spiperone binding). Interestingly, the ratio of the affinity constants for the HiAg site and the LowAg site has been used as a predictive model for IA at DA D_2 receptors.[55] This methodological approach has also been successful in the prediction of IA at cortical muscarinic receptors.[56] However, despite having a binding profile predicting IA, many of the novel phenylpiperidines were unable to stimulate presynaptic DA receptors *in vivo* as judged by measurements of DOPA accumulation (Table 2). Obviously, in contrast to some other chemical classes, the phenylpiperidines do not lend themselves to predictions of *in vivo* agonist effects by means of *in vitro* D_2 binding assays.

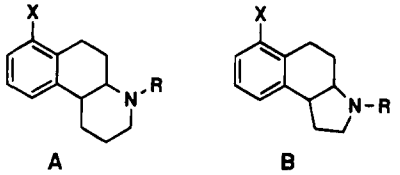
Compound **1b** has a clear-cut agonist activity at the presynaptic receptors, shown by a maximal decrease of DOPA accumulation in reserpine-pretreated rats. The lack of increase in locomotor activity indicates the absence of IA at postsynaptic receptors in contrast to, for instance, apomorphine (Table 2). These data support earlier findings by Hacksell et al.[51] In addition, some other (*S*)-(−)-phenylpiperidines seem to possess a certain, albeit weak, IA at the presynaptic receptors, shown by a slight decrease in DOPA accumulation (Table 2). The electron density in the aromatic ring appears to play an important role for the IA. This is demonstrated by compounds substituted with powerful electron-withdrawing groups (e.g., -CN and $-SO_2CH_3$) which lack IA in this assay. However, introduction of substituents with varying, albeit lower than -OH, electron-donating properties (σ_p), e.g., an -OMe (**2**), propyl group (**25**), or -H (**20**), generally yields partial agonists (Table 2). Despite the variation of electron-donating capability among these substituents, they all show a similar level of IA. Thus, some other properties, in addition to the electron-donating capability, are implicated for the expression of IA. Interestingly, the hydroxymethyl-substituted compound **8** is the most efficacious agonist next to **1b** (in reducing DOPA accumulation), despite the low electron-donating capability of this substituent (Table 2). All of the above show that the IA depends on both hydrogen bond-donating properties and the electron density in the aromatic ring. In support of this, we found that compound **9** substituted with a carboxamide (hydrogen bond-donating but simultaneously strongly electron-withdrawing properties) is completely devoid of IA.

In conclusion, to obtain maximum agonist activity for phenylpiperidines with *S*-configuration, the requirement is an aromatic substituent simultaneously possessing hydrogen bond- and electron-donating properties (i.e., -OH).

DA Antagonist Properties of the Substituted Phenylpiperidines. Table 2 contains several compounds that are dopamine receptor antagonists, as determined in the *in vivo* biochemical assays. Like haloperidol and remoxipride, they increase the synthesis (DOPA accumulation), release (DA), and metabolism (DOPAC levels) of dopamine with various efficacies and proportions between these measures.

Some compounds, e.g., **19**, **25**, **26**, and **34**, increase the locomotor activity (LMA) in actively exploring rats

Table 4. Analytical Data and Affinities at Central D_2, D_3, and 5-HT_{1A} Sites *in Vitro*



						K_i (nM)[a]			
no.	struct	X	R	isomer	formula[b]	D_2[c,d] [^{3}H]-spiperone	D_2[c,d] [^{3}H]-U-86170	D_3[c,d] [^{3}H]-spiperone	5-HT_{1A}[c,d] [^{3}H]-8-OH-DPAT
45	A	OSO_2CF_3	*n*-Pr	*cis*-(±)	$C_{17}H_{22}F_3NO_3S$·HCl	>453	744 ± 117	587 ± 52	1140
46	A	OSO_2CF_3	*n*-Pr	*trans*-(±)	$C_{17}H_{23}F_3NO_3SCl$·0.25H_2O	64 ± 8	21 ± 5	22 ± 2	39
47	B	OSO_2CF_3	*n*-Pr	*trans*-(±)	$C_{16}H_{18}F_3NO_3S$·HCl	82 ± 10	89 ± 8	61 ± 8	72 ± 4[e]
48	B	OSO_2CF_3	allyl	*trans*-(±)	$C_{16}H_{18}F_3NO_3S$·HCl	>172	125 ± 16	67 ± 3	18 ± 1.4[f]
49	B	OSO_2CF_3	allyl	*cis*-(+)	$C_{16}H_{18}F_3NO_3S$·HCl	>172	353 ± 44	173 ± 31	117 ± 15[g]
50	B	OSO_2CF_3	allyl	*cis*-(−)	$C_{16}H_{18}F_3NO_3SHCl$	>172	>1900	>500	>400
52	B	$CONH_2$	allyl	*cis*-(−)	$C_{16}H_{20}N_2O$·0.75H_2O	>172	>1500	>1500	>1000
53	B	CN	allyl	cis-(−)	$C_{16}H_{18}N_2$·HCl	>172	984 ± 74	>455	>400
54	B	OMe	allyl	*cis*-(+)		NT[h]	>339[i]	NT	>333[i]
55	B	OMe	allyl	*cis*-(−)		NT	18 ± 6[i]	NT	236 ± 28[i]
56	B	OMe	allyl	*trans*-(±)		NT	50 ± 4[i]	NT	3.7 ± 2.2[i]

[a] K_i values for displacement of the dopamine D_2 receptor antagonist spiperone, the dopamine D_2 receptor agonist U-86170, the dopamine D_3 receptor antagonist spiperone, and the 5-HT_{1A} receptor agonist 8-OH-DPAT. [b] Analyses for C, H, and N were within ±0.4%. [c] Data from cloned mammalian receptors expressed in CHO-K1 cells. [d] Values were obtained with 11 drug concentrations in which each value was determined in duplicate. [e] 5-HT_2 K_i = 36 ± 11 (ketanserin). [f] 5-HT_2 K_i = 108 ± 40 (ketanserin). [g] 5-HT_2 K_i = 212 ± 40 (ketanserin). [h] NT means not tested. [i] Data taken from ref 39.

Table 5. Effects on *in Vivo* DA Biochemistry (Striatum) and Locomotor Activity

	nonpretreated habituated rats,[a] 100 μmol/kg sc		reserpine-pretreated rats,[b] 50 μmol/kg sc		
no.	DOPAC[c]	LMA[d]	DOPA acc[e]	5-HTP acc[f]	LMA[d]
45	94 ± 6	266 ± 183	NT[g]	NT	NT
46	263 ± 15* [h,i]	200[j]	85 ± 9	62 ± 7*	211 ± 63*
47	223 ± 16* [k]	687 ± 210* [k]	NT	NT	NT
48	175 ± 12*	443 ± 107*	92 ± 6	52 ± 3*	635 ± 16*
49	108 ± 6	116 ± 34	NT	NT	NT
50	98 ± 4	148 ± 70	NT	NT	NT
53	172 ± 11*	292 ± 28* [l]	NT	NT	NT
55	314 ± 13* [m]	182 ± 51[m]	NT	NT	NT
57[n]	346 ± 29* [m,o]	354 ± 37* [m,o]	NT	NT	NT

[a] The animals were put into the activity meters and 60 min later injected sc with drug. The activity was measured for the subsequent 60 min. [b] Animals were injected with reserpine (5 mg/kg ip) 18 h, test drug 60 min, and NSD 1015 (100 mg/kg ip) 30 min before death. Controls received corresponding saline injections. Values are expressed as percent of saline controls. [c] 3,4-Dihydroxyphenylacetic acid levels in rat striatum. Values are expressed as percent of saline controls; mean ± SEM. [d] Locomotor activity. Values are expressed as percent of saline controls; means ± SEM. [e] 3,4-Dihydroxyphenylalanine accumulation in rat striatum. Values are expressed as percent of saline controls; mean ± SEM. [f] 5-Hydroxytryptophan accumulation in rat striatum. [g] NT means not tested. [h] *p < 0.05 or less. [i] Nonpretreated rats, 50 μmol/kg, DOPA accumulation (striatum) = 235 ± 5*, 5-HTP (striatum) 72 ± 4*. [j] LMA, nonpretreated rats, 50 μmol/kg: 56 ± 4*. [k] 89 μmol/kg. [l] HVA (striatum): 255 ± 13*. [m] 52 μmol/kg. [n] *cis*-(+)-5-Methoxy-1-methyl-2-(*n*-propylamino)tetralin. [o] Data taken from ref 1.

to the same level as does a high dose of apomorphine. However, compound **32** is the most efficacious LMA stimulant in habituated rats. It has since long been accepted that locomotor activity is increased when direct or indirect DA agonists stimulate postsynaptic DA receptors in the basal ganglia. The compounds under study increase the release of DA and the levels of DOPAC, as determined by the *in vivo* dialysis experiments (Table 2). This is a general effect observed for DA receptor antagonists (ref 57 and references cited therein). In this series of (*S*)-phenylpiperidines, there are a number of compounds that increase DA release to higher levels (e.g., **10**, **13**, **16**, **19**, **20**, **30**, and **33**) than does haloperidol or raclopride.[57] Compounds **10**, **19**, and **30** are also some of the most behaviorally stimulating compounds within this series. Consequently, it is tempting to suggest that this strong effect on DA release underlies the pronounced increase in LMA observed (Table 2). However, there are also compounds that are relatively weak in this aspect, exemplified by compound **23**, but still, it has strong stimulatory properties. Haloperidol releases DA to a similar level as compound **23** but produces hypomotility and catalepsy. Thus, DA release *per se* can not be the only variable responsible for the behavioral effects of DA antagonists in general. An additional explanation of this increase in locomotor activity may be the difference in ability of the (*S*)-phenylpiperidines and the classical neuroleptics to block postsynaptic DA receptors. This has been assayed in the *in vivo* Di-Pr-5,6-ADTN binding model. A general trend in this assay is that the phenylpiperidines are less efficacious than haloperidol or raclopride (Table 3; see, also, Waters et al.[43]). These data are in support of the previous suggestion that less postsynaptic antagonism favors behavioral activation. Interestingly, the non-cataleptogenic antipsychotic drug remoxipride shows similar *in vivo* binding properties as the antagonist phenylpiperidines.

Similar to the agonist-like compounds of this chemical class, the antagonists generally show low affinity to dopamine receptors in *in vitro* binding studies (Table 1, D_1 and D_4 are not shown but the IC_{50}'s are estimated to be >1000 nM for all compounds). In addition, most antagonist-like compounds (see above) have the same peculiarity as the agonistic phenylpiperidines, i.e., they show higher affinity for the HiAg state of the dopamine D_2 receptor as compared to their affinity for the LowAg state. In addition, the few examples of compounds with high affinity for D_2 receptors *in vitro*, i.e., **17**, **37**, and **41**, have weak, or no, presynaptic effects *in vivo* (Table 2). Thus, like the agonists of this chemical class, the

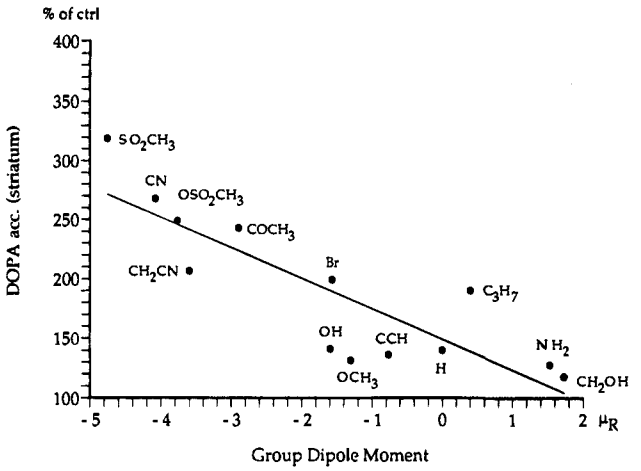


Figure 1. Relationship between DOPA accumulation (nonpretreated rats, striatum, 100 μmol/kg) and the group dipole moment (μ_R) of the aromatic 3-substituent in (*S*)-(−)-3-(3-X-phenyl)-1-propylpiperidines ($r = 0.86$, $p = 0.0002$, $n = 13$).

antagonists do not lend themselves to predictions about *in vivo* activity based on *in vitro* binding.

On the basis of the data for compounds substituted with a triflate group, we have found that antagonist activity in the *in vivo* biochemical assays seems to be sensitive for the position on the aromatic ring (Table 2). Substitution in the *meta*-position leads to an active antagonist compound, while substitution in the *ortho*- (**42**) or *para*-position (**43**) yields biochemically inactive compounds. Disubstitution with triflate groups in *meta*- and *para*-positions also leads to an inactive compound (**44**) in the *in vivo* biochemical assays. This further confirms that the *in vivo* activity is sensitive to steric bulk in the *para*-position. On the basis of the above results, it seems likely in the case of triflates that the substituent should be positioned in a *meta*-position with respect to the piperidine ring to yield compounds with antagonistic properties at DA autoreceptors *in vivo*.

To understand which subtituent properties determine the antagonistic activity of *meta*-substituted phenylpiperidines, substituents with various physical properties[58,59] were introduced. The resulting series of compounds were examined for increase of striatal DOPA or DOPAC levels (compounds **1**−**25**). It was found that introduction of a methoxy (**2**) or thiomethyl group (**15**) does not alter the *in vivo* activity relative to the unsubstituted **20** (Table 2). Compounds substituted with electron-withdrawing groups increased the levels of DOPA more than compound **20**. Thus, there seems to be an increasing ability to raise DOPA accumulation paralleled with an increase of the electron-withdrawing properties of the substituent: -H < -Br < -OSO_2CH_3 < -OSO_2CF_3 ≤ -CN < -SO_2CH_3 (Table 2). However, it is not certain whether it is the lowered electron density in the aromatic ring or the substituents themselves (hydrogen bond-accepting properties, dipole−dipole interactions[60]) which is the most important factor causing the DA receptor antagonist properties. Interestingly, when the maximal increase in DOPA accumulation in the striatum of nonpretreated rats was determined for 11 differently substituted cases, these levels were found to be correlated with the group dipole moment[60] of the substituent and displayed a near linear relationship ($r = 0.86$, $P = 0.0002$, $n = 13$, Figure 1). Likewise, a correlation between the group dipole moments and the maximal increases in DOPAC was found (nonpretreated habituated rats, $r = 0.73$, $P < 0.01$, $n = 14$). In addition, no relation between Hansch's π-parameter or Hammett's σ-values and changes in striatal DOPAC was found. These results suggest that the substituent mainly interacts directly with the receptor, i.e., *via* one or more of several possible interactions involving the substituent dipole. Therefore the electron density or distribution in the aromatic ring may be of secondary importance. This assumption is supported by the fact that compound **18**, which is substituted with a -CH_2-CN group, efficiently increases the striatal DOPA levels (Table 2). This group has only weak electron-withdrawing properties ($\sigma_m = 0.16$) but has a strong group dipole moment ($\mu_R = -3.6$, for dipole moment sign convention, see ref 60).

The low antagonistic efficacy of compounds **9** ($CONH_2$) and **17** (CHO) can not be explained by the above reasoning (Table 2), but the hydrogen bond-donating ability of compound **9** may perhaps cancel out the important interaction at the receptor. The lack of activity of the tosylate **5**, despite its electron-withdrawing character, may be a steric hindrance effect since the molar refractivity value (used as a measure of bulk of the substituent) is very high (37).[59]

The effect of replacing the *N*-propyl group in the piperidine ring with different alkyl groups or alkylaryl groups was also investigated (aromatic ring cyano-substituted compounds, **26-38**). The Et (**28**)- and *i*-Pr (**29**)-substituted compounds proved to be the most efficient to increase the DOPA accumulation (300−320%, Table 2). This observation was also made in the triflate series (**6** and **40**), but these compounds were less efficacious than the corresponding cyano analogs. The cyano-substituted secondary amines **26**, **10** (*n*-Pr), **30** (allyl), and **34** (cyclopropylmethyl) were the most efficacious in this series to increase the LMA (in nonpretreated rats, Table 2). A methyl N-substitution surprisingly yields a drug with slight inhibitory effects on the LMA in the same assay.

Compounds with N-substituents holding an aromatic system have the highest affinity for D_2 receptor sites in the *in vitro* binding assay (compounds **35-37** and **41**, Table 1). This may be due to a stabilizing effect *via* $\pi-\pi$-interactions between the ligand and an accessory binding site in the receptor. However, *in vitro* high-affinity compounds of this structural class have less antagonistic efficacy *in vivo* (Tables 2 and 3).

In conclusion, to obtain pure antagonist properties within the phenylpiperidines with the *S*-configuration, they should be substituted in the *meta*-position with respect to the piperidine ring. The group should be small, possess a strong negative dipole moment, and also lack hydrogen bond-donating properties. With respect to biochemical effects, the N-substituent should be a *n*-propyl group for maximum *in vivo* antagonist effects at the presynaptic DA receptors.

Substituted Octahydrobenzo[*f*]quinolines and Hexahydro-1*H*-benz[*e*]indoles. The interesting pharmacological properties of the substituted phenylpiperidines (e.g., **6** and **10**) encouraged us to investigate the effects of restricting the rotational freedom of the flexible phenylpiperidine system. This can be obtained by joining the piperidine 2-position with the aromatic ring by means of a two-carbon fragment, which can also

place the pseudoplane of the piperidine ring in the same plane as the aromatic ring (see below). This resulted in the synthesis of *cis* and *trans* derivatives of the 4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (compounds **45** and **46**). Previous data show that the *trans*-7-hydroxy isomer has potent central pre- and postsynaptic dopaminergic receptor agonist properties. The *cis* isomer was shown to have much less, if any, activity in tests designed to detect dopaminergic agonist activity.[61] Of the resolved enantiomers, the 4a*S*10b*S* *trans* compound was found to be the most potent, while both *cis* enantiomers were inactive as agonists.[62] The difference in dopaminergic activity between these *cis* and *trans* isomers can be rationalized on conformational grounds.[63,64] The *trans* ring system is highly rigid and overall a planar molecule, like apomorphine. Molecular modeling reveals that the *cis*-fused system is not completely rigid and can adopt two interconvertible flip conformations. In one, the amino group and the aromatic ring are synclinal, and in the other, the dopamine moiety approaches the antiperiplanar disposition and the aromatic ring approaches coplanarity with the ethylamine side chain. The deviation from overall planarity was proposed to be detrimental for an interaction with the dopamine receptor(s).[63,64]

The *in vitro* data (Table 4) show that the triflate-substituted *cis* isomer **45** displays only low affinity for D_2, D_3, and 5-HT_{1A} sites while the *trans* isomer **46** has quite a high affinity for both D_2 and D_3 receptors. A comparision of the *in vitro* data of compounds **6** and **46** indicates that the effect of restricting the rotational freedom by forming a rigid and planar system (i.e., **46**) does not increase the affinity for D_2 and D_3 receptors dramatically. The affinity for 5-HT_{1A} sites, on the other hand, increases 30-fold, as compared to **6**. This increase in 5-HT_{1A} affinity is accompanied by the appearance of agonist activity *in vivo*, i.e., **46** decreases the 5-HTP accumulation in reserpinized rats (Table 5). In contrast to the potent DA receptor agonist 7-OH and 7-OMe analogs (7-OMe[65] ED_{50} = 90 nmol/kg (DOPA accumulation, striatum) versus 130 nmol/kg for 7-OH[61]), compound **46** was inactive as an agonist, even at high doses (50 μmol/kg, Table 5). Instead, presynaptic DA receptor antagonistic properties of **46** were demonstrated by the increase in DOPAC levels in nonpretreated habituated rats. In addition, **46** increases the DOPA accumulation in striatum to 235 ± 5% (nonpretreated rats, 50 μmol/kg, $p < 0.005$). Interestingly, in the same assay, **46** decreased significantly the LMA to 56 ± 4%. This is in sharp contrast to compound **6** and indicates a stronger affinity for the postsynaptic receptors.

The *cis* isomer **45** is inactive in this assay (Table 5). Furthermore, **42**, a compound where a bulky triflate group in the *ortho*-position with respect to the piperidine ring will force this ring to adopt a conformation where its plane is nearly perpendicular to the plane of the aromatic ring, was found to be inactive. Taken together, these results suggest that the flexible phenylpiperidine **6** interacts with the DA receptor(s) in an almost coplanar conformation.

Recently, SAR on a series of 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles **1e** (BI) was reported.[39] The authors found that analogs with 6-methoxy or 6-hydroxy substituents on the aromatic ring act as dopamine receptor antagonists. The *cis* analogs were found to be more potent and selective, versus serotonergic activity, than the corresponding *trans* analogs. The methoxy substitution was found to enhance the antagonistic efficacy relative to hydroxy substitution. It was also shown that the antagonistic activity resides in the 3a*R* (−)-enantiomers. These results are in line with what has been reported for *cis*- and *trans*-2-amino-5-methoxy-1-methyltetralins, here exemplified by **1a**.[2]

Introduction of a triflate group on the aromatic ring in the series of BI's with a *trans* junction (**47** and **48**) leads to slightly lower affinity for D_2 and 5-HT_{1A} receptors as compared to the corresponding methoxy analog **56**. These compounds were also found to display some preference for the DA D_3 receptor *in vitro*. Compound **48** was found to be inactive as a DA agonist, while a partial decrease in 5-HTP accumulation in reserpinized rats was observed at 50 μmol/kg (sc). This indicates intrinsic activity at the 5-HT_{1A} receptor (Table 5). In nonpretreated habituated rats, **47** and **48** increased the DOPAC levels as well as the LMA (Table 5). Thus, **47** and **48** appear to be antagonists at the presynaptic DA receptors.

Triflate substitution of compounds with the *cis* junction (**49** and **50**) leads to loss of *in vitro* affinity for D_2, D_3, and 5-HT_{1A} receptors. This is accompanied by a loss in *in vivo* activity both behaviorally and biochemically. The cyano analog **53** weakly increased the DOPAC levels in nonpretreated habituated rats. These results are intriguing since the corresponding methoxy analog **55** is the most efficient in that sense. It appears that the presence of an electron-attracting group diminishes the *in vivo* activity for the *cis*-BI analogs (e.g., OMe versus CN) and an increase in the bulkiness abolished all activity (e.g., OSO_2CF_3). The difference in activity between the methoxy and cyano analogs may be attributed to the difference in lipophilic properties rather than electronic properties since the methoxy group is more lipophilic than the cyano group.[58] It is of particular interest to note that the trend for the antagonist-like activity in the biochemical assays *in vivo* is OMe > CN ≫ OTf for the *cis*-(−)-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles, which has also been found to be valid for the 5-substituted *cis*-(+)-2-amino-1-methyltetralins.[17]

In conclusion, for triflate-substituted octahydrobenzo[*f*]quinolines and benz[*e*]indoles, the *trans* isomers displayed similar pharmacological properties as the corresponding phenylpiperidines whereas the *cis* isomers of the former are inactive. Both of the above *trans* structures have the basic N atom in, or near, the plane of the aromatic ring.[66] This suggests that the active antagonist conformation of the flexible phenylpiperidines is the one where the two rings are coplanar, or nearly so. The dependence on the aromatic substituent for the presynaptic antagonism of the *cis*-benz[*e*]indoles shows the same trend as for the 5-substituted *cis*-(1*S*)-methyl-(2*R*)-aminotetralins. This suggests that these latter structural classes interact similarly with the DA autoreceptors but differently from the interaction exerted by the phenylpiperidines.

Experimental Section

General. ^1H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 300 and 75.4 MHz, respectively, using a Varian XL 300 spectrometer. The spectra for the amines were recorded on

the free bases. Chemical shifts are reported as δ values (ppm) relative to an internal standard (tetramethylsilane). Low-resolution mass spectra were recorded on a HP 5970A instrument operating at an ionization potential of 70 eV. The mass detector was interfaced with a HP5700 gas chromatograph equipped with a fused silica column (11 m 0.22 mm i.d.) coated with cross-linked SE-54 (film thickness 0.3 mm, He gas, flow 40 cm/s). Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden. Melting points were determined with a melting point microscope (Reichert Thermovar) and are uncorrected. For flash chromatography, silica gel 60 (0.040–0.063 mm, E. Merck, No. 9385) was used. The amine products were converted into their corresponding HCl salts by dissolving the free base in an ethanolic HCl solution. The solvent was removed and azeotroped with absolute ethanol or toluene *in vacuo* followed by recrystallization from an appropriate solvent. The fumarate salts were prepared using a similar procedure, substituting HCl for fumaric acid.

Materials. All chemicals used are commercially available and were used without further purification. (*S*)-(−)-3-(3-Hydroxyphenyl)-1-propylpiperidine (**1b**) was synthesized by Astra Södertälje using the literature method.[67] The 3-(tributylstannyl)thiophene was synthesized according to the literature method.[68]

(*S*)-(−)-3-(3-Methoxyphenyl)-1-propylpiperidine (2) (Scheme 1). A solution of **1b** (220 mg, 1 mmol), triethylamine (3 mg, 0.03 mmol), and ground sodium hydroxide (100 mg, 2.58 mmol) in 10 mL of THF was stirred at room temperature for 30 min.[18] The temperature was then increased to 30 °C and dimethyl sulfate (129 mg, 1.02 mmol; Warning! Dimethyl sulfate is acutely toxic and also carcinogenic!) was added over a period of about 1.5 h, maintaining the reaction temperature at 25–30 °C by external cooling. The reaction mass was subsequently digested at about 60 °C for 2 h. Most of the conversion takes place prior to digestion and digestion is mainly intended to destroy unreacted dimethyl sulfate. Water (20 mL) was then added and the mixture stirred overnight at room temperature. The aqueous phase was extracted with diethyl ether (three portions), the combined organic phases were washed with brine (2 × 5 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica column using MeOH:CH_2Cl_2 (1:9 (v/v)) as eluent. Concentration of the pooled fractions afforded 205 mg (88%) of pure **2.** The amine was converted to the hydrochloride salt using HCl-saturated ethanol and then recrystallized from ethanol/isopropyl ether. This product has been characterized elsewhere:[52] mp 202–206 °C (HCl, lit mp 200.5–202 °C); MS *m/z* (rel intensity, 70 eV) 233.15 (M^+, 5.2), 204.15 (100), 121.05 (15.5), 90.95 (15.3), 70.05 (20.1).

(*S*)-(−)-1-Propyl-3-[3-(2,2,2-trifluoroethoxy)phenyl]piperidine (3) (Scheme 1). A three-necked round-bottomed flask equipped with a dropping funnel and a magnetic stirring bar was charged with sodium hydride dispersion (60% active, 332 mg, 8.66 mmol in mineral oil). The hydride was washed with *n*-hexane (2 × 5 mL) and suspended in 10 mL of anhydrous DMF. Compound **1b** (1.86 g, 8.49 mmol), dissolved in anhydrous DMF (30 mL), was slowly added over a period of 45 min. The mixture was then stirred at 40 °C for 1 h, under a nitrogen atmosphere, followed by dropwise addition of 2,2,2-trifluoroethyl *p*-toluenesulfonate (2.27 g, 8.91 mmol) dissolved in 20 mL of DMF.[69] The mixture was then stirred at 80 °C for 20 h. The reaction mixture was then cooled and poured into an ice/water mixture and the aqueous solution extracted with diethyl ether (4 × 30 mL). The combined etheral extracts were washed with a 5% aqueous sodium hydroxide solution and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (petroleum ether:ethyl acetate:Et_3N, 85:10:5 (v/v)), which, after concentration of the pooled fractions, afforded 790 mg (31%) of the title compound as a colorless oil. The amine was converted into the hydrochloride salt and recrystallized from ethanol/diethyl ether: mp 156–160 °C (HCl); ^{1}H-NMR (300 MHz, D_2O) δ 1.0 (t, 3H), 1.7–2.2 (m, 6H), 2.85–3.2 (m, 5H), 3.6 (m, 2H), 4.6 (q, *J* = 8.7 Hz, 2H), 7.05 (m, 3H), 7.4 (t, *J* = 7.6 Hz, 1H); MS *m/z* (rel intensity, 70 eV) 301.15 (M^+, 4.2), 273.05 (15.8), 272.15 (100), 189.05 (12.5), 86.10 (9.7), 70.20 (10.8); $[\alpha]^{20}_D$ −6.7° (*c* 1.0, MeOH).

(*S*)-(−)-3-Methanesulfonic Acid 3-(1-Propylpiperidin-3-yl)phenyl Ester (4) (Scheme 1). A solution of **1b** (200 mg, 0.91 mmol) and triethylamine (101 mg, 1 mmol) in 15 mL of CH_2Cl_2 was cooled to 0 °C. Then mesyl chloride (136 mg, 1.19 mmol) dissolved in 5 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to reach room temperature and then stirred for 2 h at 25 °C. The reaction was finally quenched with water. The organic layer was separated and washed with 10% HCl and then 10% Na_2CO_3. After drying ($MgSO_4$), the solvent was removed under reduced pressure. The residue was chromatographed on a silica column using MeOH:CH_2Cl_2 (1:12 (v/v)) as eluent. The fractions containing pure **4** were collected, and the solvent was removed *in vacuo*, affording 238 mg (88%) of an oil. The amine was then converted into the fumarate salt and recrystallized from ethanol: mp 164–165 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.35–2.0 (m, 8H), 2.33 (m, 2H), 2.82–3.0 (m, 3H), 3.14 (s, 3H), 7.1–7.4 (m, 4H); MS *m/z* (rel intensity, 70 eV) 297.05 (M^+, 2.1), 269.05 (14.6), 268.05 (100), 189.1 (34.5), 188.1 (10.2), 120.0 (8.6); $[\alpha]^{20}_D$ −11.6° (*c* 1.0, MeOH).

(*S*)-(−)-Toluene-4-sulfonic Acid 3-(1-Propylpiperidin-3-yl)phenyl Ester (5) (Scheme 1). This compound was prepared as described for **4**, using **1b** (150 mg, 0.68 mmol), *p*-toluenesulfonyl chloride (196 mg, 1.02 mmol), and pyridine (107 mg, 1.36 mmol).[19] Purification of the crude product by flash chromatography (CH_2Cl_2:MeOH, 9:1 (v/v)) afforded 199 mg (78%) of pure **5**. The amine was converted into the HCl salt and recrystallized from ethanol/diethyl ether: mp 154 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.25 (qd, *J* = 12.2, 4.5 Hz, 1H), 1.4–2.0 (m, 7H), 2.3 (m, 2H), 2.45 (s, 3H), 2.7 (tt, *J* = 11.7, 3.6 Hz, 1H), 2.9 (m, 2H), 6.7 (s, 1H), 6.9 (dd, *J* = 8, 2.5 Hz, 1H), 7.1 (d, *J* = 7.6 Hz, 1H), 7.2 (t, *J* = 7.6 Hz, 1H), 7.3 (d, *J* = 8.7 Hz, 2H), 7.7 (d, *J* = 9.2 Hz, 2H); MS *m/z* (rel intensity, 70 eV) 373.15 (M^+, 2.0), 345.15 (21.1), 344.15 (100), 218.1 (12.2), 189.1 (35.7), 188.1 (11.8); $[\alpha]^{20}_D$ −4.3° (*c* 1.0, MeOH).

(*S*)-(−)-Trifluoromethanesulfonic Acid 3-(1-Propylpiperidin-3-yl)phenyl Ester (6) (Scheme 1). A solution of **1b** (3.3 g, 15.07 mmol) and triethylamine (1.68 g, 16.58 mmol) in 300 mL of CH_2Cl_2 was cooled to −30 °C. Then triflic anhydride (4.68 g, 16.58 mmol) in 30 mL of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 2 h at 25 °C. The reaction was quenched with cold water and the organic layer separated and washed with two portions of cold 5% HCl solution. Following a wash of the organic portion with brine and drying ($MgSO_4$), the solvent was removed under reduced pressure and the residue was chromatographed on a silica column with MeOH:CH_2Cl_2 (1:19 (v/v)) as eluent. The solvents from the collected fractions containing pure **6** were evaporated yielding a pale oil 4.87 g (92%). Addition of ethanolic HCl to an etheral solution afforded **6**·HCl. This product has been characterized elsewhere:[3] mp 156–159 °C (HCl).

(*S*)-(−)-3-(1-Propylpiperidin-3-yl)benzoic Acid Methyl Ester (7) (Scheme 1). A mixture of compound **6** (5.5 g, 15.67 mmol), triethylamine (3.17 g, 31.34 mmol), MeOH (20 g, 626.8 mmol), $Pd(OAc)_2$ (0.105 g, 0.47 mmol), and 1,3-bis(diphenylphosphino)propane (0.194 g, 0.47 mmol) in 60 mL of DMSO was stirred at room temperature for 15 min or until all particles were dissolved.[20] A stream of CO(g) (Caution! Highly toxic!) was passed through the solution for 4–5 min, and then the reaction vessel was placed under a slightly positive pressure of CO(g) (1 atm). The temperature was increased to 70 °C (oil bath). After 6 h, GC analysis revealed the complete absence of any **6** and indicated **7** as the major product (see the Discussion). The reaction mixture was allowed to cool to room temperature. Water (200 mL) was then added, and the aqueous solution was extracted with five portions of diethyl ether. The combined organic phases were washed with water until neutral, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica column using MeOH:CH_2Cl_2 (1:12 (v/v)) as eluent. The solvents from the collected fractions containing pure **7** were evaporated yielding 3.43 g (84%). The amine was converted into the hydrochloride salt and recrystal-

lized from ethanol/isopropyl ether: m.p 166–67 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.4–2.1 (m, 8H), 2.3 (m, 2H), 2.9 (tt, 1H), 3.0 (m, 2H), 3.9 (s, 3H), 7.36 (t, J = 7.62 Hz, 1H), 7.41 (dt, J = 7.8, 1.5 Hz, 1H), 7.88 (dt, J = 7.5, 1.6 Hz, 1H), 7.9 (t, J = 1.3 Hz, 1H); MS m/z (rel intensity, 70 eV) 261.15 (M^+, 3.0), 233.05 (16.2), 232.05 (100), 100.55 (12.8), 86.05 (7.3); $[\alpha]^{20}_D$ −6.6° (c 1.0, MeOH).

(*S*)-(−)-[3-(1-Propylpiperidin-3-yl)phenyl]methanol (8) (Scheme 1). A solution of **7** (396 mg, 1.51 mmol) in 30 mL of dry diethyl ether was cooled to 0 °C. Solid $LiAlH_4$ (400 mg, 10.5 mmol) was then added in small portions.[70] The mixture was stirred for 1 h at 0 °C. The reaction was then terminated by the addition of 1 mL of water, 1 mL of 15% sodium hydroxide solution, and finally 3 mL of water. The resulting mixture was filtered through a pad of Celite, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on a silica column with MeOH:CH_2Cl_2 (1:3 (v/v)) as eluent. The solvents from the collected fractions containing pure **8** were evaporated yielding 293 mg (83%) as an oil. The amine was converted into the hydrochloride salt and recrystallized from ethanol/isopropyl ether: m.p 144–148 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.4–2.0 (m, 8H), 2.25 (m, 2H), 2.7 (br s, 1H), 2.85 (tt, 1H), 2.95 (m, 2H), 4.7 (s, 2H), 7.1 (d, 1H), 7.2–7.3 (m, 3H); MS m/z (rel intensity, 70 eV) 233.15 (M^+, 3.7), 205.20 (14.3), 204.1 (100), 131.0 (6.0), 86.0 (6.9); $[\alpha]^{20}_D$ −7.9° (c 1.0, MeOH).

(*S*)-(−)-3-(1-Propylpiperidin-3-yl)benzamide (9) (Sceme 1). A solution of **7** (12.0 g, 46 mmol) and freshly distilled formamide (7.23 g, 161 mmol) in DMF (150 mL) was heated to 100 °C under a blanket of argon. Sodium methoxide (14.6 g, 82.8 mmol) in methanol (30%) was added dropwise over 30 min under continuous stirring.[23] After 1 h, GC analysis revealed the complete absence of **7** and indicated **9** as the sole product. The reaction mixture was then allowed to reach room temperature. To the reaction mixture was then added 2-propanol (700 mL), and the resulting solution was filtered through a pad of Celite and evaporated to dryness. The residue was chromatographed on a silica column using CH_2Cl_2:MeOH (9:1 + 1% NEt_3 (v/v)) as eluent. Collection of the fractions containing pure product followed by evaporation of the solvent afforded 9.6 g of **9** as an oil (84%) which crystallized on standing: mp 130 °C (free base); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.45–1.6 (m, 2H), 1.7–1.88 (m, 2H), 1.92–2.1 (m, 4H), 2.35 (m, 2H), 2.85–3.1 (m, 3H), 5.8 (br s, 1H), 6.1 (br s, 1H), 7.35–7.46 (m, 2H), 7.65 (dt, J = 7.5, 1.5 Hz, 1H), 7.76 (s, 1H); MS m/z (rel intensity, 70 eV) 246.15 (M^+, 2.7), 217.15 (100), 131.05 (23.1), 100.55 (18.8), 70.05 (19.5); $[\alpha]^{20}_D$ −7.4° (c 1.0, CH_2Cl_2).

(*S*)-(−)-3-(1-Propylpiperidin-3-yl)benzonitrile (10) (Scheme 1). A solution of **9** (6.5 g, 26.4 mmol) and freshly distilled $POCl_3$ (6 mL, 66 mmol) in dry DMF (50 mL) was heated at 80 °C for 3 h under an argon atmosphere.[24] Evaporation of the solvent yielded a dark, oily residue, which was dissolved in water. The solution was then basified with a saturated sodium carbonate solution and extracted several times with CH_2Cl_2. The combined organic layers were evaporated under reduced pressure, and the residue was purified by flash chromatography (acetone:MeOH, 20:1 (v/v)), affording 5.5 g (92%) of pure **10** as an oil. The amine was converted to the hydrochloride salt using HCl-saturated ethanol and then recrystallized from ethanol/isopropyl ether affording the pure salt. This compound has been characterized elsewhere:[3] mp 197–199 °C (HCl).

(*S*)-(−)-3-(1-Propylpiperidin-3-yl)phenylamine (11) (Scheme 1). To a solution of **7** (10 g, 38.31 mmol) in concentrated sulfuric acid (240 mL) and CH_2Cl_2 (400 mL) was added carefully sodium azide (15 g, 231 mmol). After the addition was completed, the mixture was brought to reflux (50 °C). Over a period of 6 h, small portions of additional sodium azide (3 × 2 g) were added to the reaction mixture.[25] After refluxing for a further 20 h, the reaction mixture was cooled to room temperature and the reaction quenched with ice water. The aqueous solution was basified with 20% NaOH, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 7.12 g (85%) of crude **11** (95% pure according to GLC), which was used in subsequent steps without further purification. A small sample (200 mg) was purified by flash chromatography (CH_2Cl_2:MeOH, 9:1 (v/v)), affording 178 mg (76%) of pure **11** as an oil (the HCl salt is highly hygroscopic): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.45–2.2 (m, 8H), 2.45 (m, 2H), 2.9 (tt, 1H), 3.1 (m, 2H), 3.75 (br s, 2H), 6.5–6.65 (m, 3H), 7.1 (t, J = 8.3 Hz, 1H); MS m/z (rel intensity, 70 eV) 218.45 (M^+, 13.2), 190.4 (13.4), 189.4 (100), 120.25 (19.1), 70.15 (19.0); $[\alpha]^{20}_D$ −7.0° (c 1.0, CH_2Cl_2, base).

(*S*)-(+)-*C,C,C*-Trifluoro-*N*-[3-(1-propylpiperidin-3-yl)-phenyl]methanesulfonamide (12) (Scheme 1). This compound was prepared as described for **6**, using **11** (230 mg, 1.05 mmol) and triflic anhydride (326 mg, 1.16 mmol). Purification of the crude product by flash chromatography (CH_2Cl_2:MeOH, 9:1 (v/v)) afforded 176 mg (48%) of pure **12**, which crystallized on standing: mp 124–128 °C (free base); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.4–2.3 (m, 5H), 2.6 (m, 2H), 2.8–3.1 (m, 3H), 3.3 (m, 2H), 3.75 (m, 1H), 6.7 (d, 1H), 7.0 (m, 1H), 7.2–7.4 (m, 2H); MS m/z (rel intensity, 70 eV) 350.2 (M^+, 2.6), 322.15 (16.2), 321.15 (100), 188.25 (12.3), 187.25 (20.0); $[\alpha]^{20}_D$ +123.8° (c 1.0, CH_2Cl_2, free base).

(*S*)-(−)-3-(3-Bromophenyl)-1-propylpiperidine (13) (Scheme 1). To a solution of **11**·HCl (16.28 g, 55.96 mmol) in 100 mL of 48% aqueous HBr at 0 °C was added dropwise with stirring a solution of sodium nitrite (4.2 g, 60.96 mmol) in 4 mL of water.[26] The reaction mixture was stirred for 1 h at 0 °C under an argon atmosphere. Cuprous bromide (8.2 g, 57.16 mmol) dissolved in 20 mL of 48% HBr was than added and the solution heated at 80 °C for 40 min. After cooling, 100 mL of water was added and the reaction mixture was made alkaline using concentrated aqueous ammonia. The aqueous solution was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated *in vacuo* to give 13.6 g (85%) of crude **13**. The residue was purified by flash chromatography using CH_2Cl_2:MeOH (9:1 (v/v)) as eluent, affording pure **13** (9.05 g, 57.3%). The amine was converted to the hydrochloride salt with ethanolic HCl and recrystallized from ethanol/isopropyl ether: mp 209–211 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.33–2.0 (m, 8H), 2.3 (m, 2H), 2.81 (tt, J = 11.4, 3.3 Hz, 1H), 2.97 (m, 2H), 7.15 (d, J = 4.8 Hz, 2H), 7.32 (dt, J = 4.4, 2.0 Hz, 1H), 7.37 (br, s, 1H); MS m/z (rel intensity, 70 eV) 283.05 (M^+ + 1, 2.8), 282.05 (M^+, 1.9), 281.05 (M^+ − 1, 3.4), 253.95 (94.2), 251.95 (100), 129.95 (30.8), 128.95 (31.7); $[\alpha]^{20}_D$ −7.9° (c 1.0, MeOH).

(*S*)-(−)-*N,N*-Dimethyl-3-(1-propylpiperidin-3-yl)benzenesulfonamide (14) (Scheme 2). To a solution of **13** (700 mg, 2.49 mmol) in dry THF (20 mL), at −78 °C, was added a solution of *sec*-butyllitium in hexane (1.4 M, 2.66 mL, 3.73 mmol). The mixture was stirred at −78 °C for 15 min and then allowed to reach 0 °C. After an additional 30 min at 0 °C, the solution was brought to −78 °C. Dry sulfur dioxide gas was passed into the reaction vessel for 20 min *via* a needle positioned just above the surface of the solution and gave a copious precipitate.[71] The reaction mixture was then allowed to reach room temperature and stirred for 1 h under a sulfur dioxide atmosphere. The reaction mixture was concentrated *in vacuo* and pretreated with CH_2Cl_2 (25 mL). The suspension was cooled to 0 °C and $SOCl_2$ (3 mL) was added dropwise. After 2 h, the mixture was concentrated *in vacuo* to remove excess of $SOCl_2$. The oily residue was redissolved in CH_2Cl_2 (35 mL) and added dropwise to a water solution of dimethylamine (25 mL, 40% water solution).[72] The mixture was then brought to reflux for 3 h under vigorous stirring. The phases were separated, and the water phase was extracted several times with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography using CH_2Cl_2:MeOH (9:1 (v/v)) as eluent, affording pure **14** (603 mg, 38%). The amine was converted to the fumarate salt and recrystallized from ethanol/isopropyl ether: mp 162–164 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.45–1.6 (m, 3H), 1.7–1.85 (m, 2H), 1.92–2.1 (m, 3H), 2.35 (m, 2H), 2.7 (s, 6H), 2.85–3.1 (m, 3H), 7.45–7.65 (m, 4H); MS m/z (rel

intensity, 70 eV) 310.10 (M^+, 2.9), 282.10 (17.0), 281.10 (100), 173.10 (12.3), 129.0 (10.5); $[\alpha]^{20}_D$ −6.8° (*c* 1.0, CH_2Cl_2).

(*S*)-(−)-3-[3-(Methylsulfanyl)phenyl]-1-propylpiperidine (15) (Scheme 2). Compound **13** (5 g) was distilled at 145 °C (0.2 mbar, Kugelrohr distillation) yielding 4.6 g (16.5 mmol) of pure **13** which then was dissolved in dry diethyl ether (150 mL). The solution was cooled to −78 °C, and *tert*-butyllitium in hexane (1.7 M, 12.63 mL, 21.47 mmol) was added dropwise. The resulting mixture was stirred at −78 °C for 15 min, allowed to warm to 0 °C, stirred for additional 30 min at 0 °C, and brought to −78 °C and then treated with freshly distilled dimethyl disulfide (2.5 mL, 26.5 mmol). The reaction mixture was then allowed to reach room temperature and stirred for 1 h. The reaction mixture was then diluted with 10% Na_2CO_3, and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 3.87 g (94%) of crude **15**. The residue was purified by flash chromatography using CH_2Cl_2:MeOH (12:1 (v/v)) as eluent, affording pure **15** (2.61 g, 81%). The amine was converted to the fumarate salt and recrystallized in ethanol/isopropyl ether: mp 184 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.0 (t, 3H), 1.6−2.1 (m, 5H), 2.5 (s, 3H), 2.6−2.7 (m, 3H), 2.9 (m, 2H), 3.55 (m, 3H), 7.0 (d, 1H), 7.1−7.3 (m, 3H); MS *m/z* (rel intensity, 70 eV) 249.25 (M^+, 7.9), 221.15 (15.3), 220.15 (100), 150.15 (5.2), 129.15 (7.3); $[\alpha]^{20}_D$ −9.4° (*c* 1.0, MeOH).

(*S*)-(−)-3-[3-(Methylsulfonyl)phenyl]-1-propylpiperidine (16) (Scheme 2). To a solution of **15** (1.7 g, 6.83 mmol) in trifluoroacetic acid (20 mL) was added a solution of *m*-chloroperoxybenzoic acid (2.71 g, 15.7 mmol) in trifluoroacetic acid (20 mL).[73] The mixture was stirred at room temperature for 3 h and poured into ice water. The resulting mixture was made alkaline with 15% NaOH and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* (1.35 g, 71%). The oily residue was purified by flash chromatography using CH_2Cl_2: MeOH (9:1 (v/v)) as eluent, affording pure **16** (1.0 g, 52%). The amine was converted into the HCl salt and recrystallized in ethano/isopropyl ether: mp 181 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.45−1.6 (m, 3H), 1.7−1.85 (m, 2H), 1.9−2.0 (m, 3H), 2.3 (m, 2H), 2.9−3.1 (m, 3H), 3.1 (s, 3H), 7.5 (m, 2H), 7.8 (m, 2H); MS *m/z* (rel intensity, 70 eV) 281.25 (M^+, 2.9), 253.15 (16.1), 252.15 (100), 129.15 (9.6), 70.15 (6.4); $[\alpha]^{20}_D$ −6.1° (*c* 1.0, MeOH).

The water phase above was evaporated to dryness, and the resulting salt was redissolved in absolute ethanol (50 mL). Nonsoluble particles were filtered off, and the solution was concentrated *in vacuo* yielding a residue (800 mg, one spot on TLC) which was redissolved in CH_3CN (20 mL). To the *N*-oxide solution was added $TiCl_4$ (507 mg, 2.68 mmol) and NaI (1.2 g, 8.05 mmol).[28] The reaction mixture turned dark brown almost immediately, and TLC, after 40 min, confirmed complete reaction. The reaction was interrupted by adding 10% KOH (30 mL). The water phase was extracted with diethyl ether (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was further purified as above yielding 310 mg (41%) of pure **16**.

(*S*)-(−)-3-(1-Propylpiperidin-3-yl)benzaldehyde (17) (Scheme 2). To a solution of **13** (3.45 g, 12.3 mmol) in dry diethyl ether (40 mL) at −78 °C was added a solution of *tert*-butyllitium in hexane (1.7 M, 8 mL, 13.5 mmol). The mixture was stirred at −78 °C under an argon atmosphere for 15 min and allowed to warm to 0 °C. After an additional 30 min at 0 °C, the solution was brought to −78 °C and dry dimethylformamide (1.1 mL, 15.9 mmol) was added. The reaction mixture was allowed to reach room temperature and stirred for 1 h. The reaction mixture was then diluted with 10% Na_2CO_3, and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 2.72 g (96%) of crude **17**. The residue was purified by flash chromatography using CH_2Cl_2: MeOH (9:1 (v/v)) as eluent, affording pure **17** (2.12 g, 75%). The amine was converted to the hydrochloride salt with etheral HCl. The **17**·HCl was recrystallized in ethanol/isopropyl ether: mp 166−68 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.45−1.6 (m, 3H), 1.7−1.85 (m, 2H), 1.9−2.0 (m, 3H), 2.3 (m, 2H), 2.85−3.1 (m, 3H), 7.35−7.5 (m, 2H), 7.7−7.9 (m, 2H), 10.0 (s, 1H); MS *m/z* (rel intensity, 70 eV) 231.15 (M^+, 3.6), 203.2 (14.3), 202.2 (100), 131.10 (17.5), 91 (12.4); $[\alpha]^{20}_D$ −6.0° (*c* 1.0, MeOH).

(*S*)-(−)-[3-(1-Propylpiperidin-3-yl)phenyl]acetonitrile (18) (Scheme 2). A solution of tosylmethyl isocyanide[29] (446 mg, 2.29 mmol) in 1,2-dimethoxyethane (distilled from $LiAlH_4$, 10 mL) was added dropwise to a stirred suspension of potassium *tert*-butylate (500 mg, 4.45 mmol) in 10 mL of 1,2-dimethoxyethane. The reaction mixture was kept below −30 °C under nitrogen. Then a solution of **17** (500 mg, 2.16 mmol) in 15 mL of 1,2-dimethoxyethane was added dropwise to the mixture at −50 to −60 °C. After 60 min, methanol (6 mL) was added to the cold solution, which was then heated to reflux for 20 min. The solution was evaporated to dryness, and the residue was taken up in 10% HCl solution (30 mL). The water phase was extracted with CH_2Cl_2, and the combined organic phases were washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 850 mg (160%) of crude **18**. The residue was purified by flash chromatography using CH_2Cl_2:MeOH (9:1 (v/v)) as eluent, affording pure **18** (261 mg, 50%). The amine was converted to the fumarate salt and crystallized in ethanol/isopropyl ether: mp 112−119 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (t, 3H), 1.3−1.5 (m, 3H), 1.6−1.8 (m, 2H), 1.9−2.0 (m, 3H), 2.3 (m, 2H), 2.82 (tt, J = 11.5, 3.7 Hz, 1H), 2.95 (m, 2H), 3.7 (s, 2H), 7.1−7.35 (m, 4H); MS *m/z* (rel intensity, 70 eV) 242.05 (M^+, 2.3), 214.1 (15.4), 213.1 (100), 130.00 (12.6), 115.0 (9.7); $[\alpha]^{20}_D$ −12.2° (*c* 1.0, MeOH).

(*S*)-(−)-3-(3-Ethynylphenyl)-1-propylpiperidine (19) (Scheme 3). To a solution of **6** (1.2 g, 3.41 mmol) in 20 mL of 1,4-dioxane were added tri-*n*-butylethenylstannane (1.13 g, 3.58 mmol), LiCl (446 mg, 10.2 mmol), $Pd(PPh_3)_4$ (78.7 mg, 0.068 mmol), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol.[31] The resulting mixture was refluxed under nitrogen for 6 h, cooled to room temperature, and treated with 1 mL of pyridine and 2 mL of pyridinium fluoride. The resulting mixture was stirred at room temperature for 16 h. The mixture was diluted with diethyl ether, filtered through a small pad of Celite, and washed with water, 10% HCl, and concentrated sodium chloride solution. The organic phase was dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography using acetone:MeOH (25:1 (v/v)) as eluent, affording pure **19** (400 mg, 52%). The amine was converted into the hydrochloride and recrystallized from ethanol/isopropyl ether: mp 172−174 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H), 1.4−2.0 (m, 8H), 2.31 (m, 2H), 2.81 (tt, 1H), 2.98 (m, 2H), 3.05 (s, 1H), 7.2−7.45 (m, 4H); MS *m/z* (rel intensity, 70 eV) 227.1 (M^+, 5.2), 199.1 (15.4), 198.1 (100), 128.05 (15.7), 15.05 (20.7), 70.05 (9.2); $[\alpha]^{20}_D$ −9.7° (*c* 1.0, MeOH).

(*S*)-(−)-3-Phenyl-1-propylpiperidine (20) (Scheme 3). To a stirred solution of **6** (500 mg, 1.42 mmol) in DMF (20 mL) under an argon atmosphere at room temperature were sequentially added triethylamine (575 mg, 5.68 mmol), formic acid (261 mg, 5.68 mmol), PPh_3 (74.4 mg, 0.28 mmol), and $Pd(OAc)_2$ (47.8 mg, 0.21 mmol).[33] The reaction temperature was raised to 60 °C. After 6 h, the reaction was complete (GLC) and the reaction mixture was cooled to room temperature; 5% HCl (30 mL) was added, and after another 0.5 h of stirring, the mixture was poured into CH_2Cl_2 (75 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with water until neutrality, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2: MeOH, 9:1 (v/v)), affording 204 mg (71%) of pure **20** as an oil: mp 195−200 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H), 1.4−2.0 (m, 8H), 2.35 (m, 2H), 2.82 (tt, 1H), 3.05 (m, 2H), 7.2−7.35 (m, 5H); MS *m/z* (rel intensity, 70 eV) 203.2 (M^+, 5.0), 175.1 (12.6), 174.1 (100), 91.05 (16.1), 70.05 (7.9); $[\alpha]^{20}_D$ −4.7° (*c* 1.0, MeOH).

(*S*)-(−)-1-Propyl-3-*m*-tolylpiperidine (21) (Scheme 3). This compound was prepared as described for **19** from **6** (1.06

g, 3.02 mmol) and tetramethylstannane (0.57 g, 3.18 mmol). Purification of the crude reaction mixture by flash chromatography (acetone:MeOH, 20:1 (v/v)) afforded 380 mg (58%) of pure **21**. The amine was converted into the hydrochloride salt and recrystallized from ethanol/isopropyl ether: mp 193–196 °C (HCl); ^{1}H-NMR (300 MHz, D_2O, HCl salt) δ 0.95 (t, 3H), 1.7–2.15 (m, 6H), 2.35 (s, 3H), 2.9–3.15 (m, 5H), 3.6 (m, 2H), 7.1–7.25 (m, 3H), 7.32 (t, J = 7.8 Hz, 1H); MS *m/z* (rel intensity, 70 eV) 217.15 (5.1, M^+), 189.15 (14.4), 188.15 (100), 105.05 (18.2), 70.05 (14.5); $[\alpha]^{20}_D$ −5.8° (*c* 1.0, MeOH).

(*S*)-(−)-1-Propyl-3-(3-thiophene-3-ylphenyl)piperidine (22) (Scheme 3). This compound was prepared as described for **19** from **6** (1.22 g, 3.47 mmol), 3-(tributylstannyl)-thiophene[68] (1.55 g, 4.16 mmol), $(PPh_3)_2PdCl_2$ (195 mg, 0.28 mmol), and PPh_3 (146 mg, 0.56 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 12:1 (v/v)) afforded 690 mg (70%) of pure **22** as an oil. The amine was converted into the hydrochloride salt and recrystallized from ethanol/isopropyl ether: mp 155–160 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.4–2.1 (m, 8H), 2.3 (m, 2H), 2.85 (tt, 1H), 3.0 (m, 2H), 7.07 (dd, J = 3.6 Hz, 1H), 7.15 (dt, J = 7.7 Hz, 1H), 7.24–7.33 (m, 3H), 7.43 (t, J = 1.8 Hz, 1H), 7.47 (d, J = 1.2 Hz, 1H); MS *m/z* (rel intensity, 70 eV) 285.1 (M^+, 7.2), 257.1 (20.1), 256.1 (100), 186.00 (15.8), 173.0 (14.8), 128.0 (20.5); $[\alpha]^{20}_D$ −3.0° (*c* 1.0, MeOH).

(*S*)-(−)-1-[3-(1-Propylpiperidin-3-yl)phenyl]ethanone (23) (Scheme 3). To a stirred solution of **6** (1.87 g, 5.34 mmol) in DMF (18 mL) under an argon atmosphere at room temperature was sequentially added triethylamine (1.63 g, 16 mmol), butyl vinyl ether (4.01 g, 40 mmol), 1,3-bis(diphenylphosphino)propane (309 mg, 0.749 mmol), and $Pd(OAc)_2$ (129 mg, 0.575 mmol).[34] The reaction flask was heated to 80 °C. After 0.5 h, the conversion was complete (GLC) and the reaction mixture was cooled to room temperature; 5% HCl (30 mL) was added, and after another 0.5 h of stirring, the mixture was poured into CH_2Cl_2 (60 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with water until neutrality, dried (anhydrous $MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2:MeOH, 9:1 (v/v)), affording pure **23** (964 mg, 74%). The amine was converted into the hydrochloride salt and recrystallized from ethanol/isopropyl ether: mp 151–156 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.4–2.1 (m, 8H), 2.2 (m, 2H), 2.25 (s, 3H), 2.95 (tt, 1H), 3.0 (m, 2H), 7.2–7.4 (m, 2H), 7.6–7.8 (m, 2H); MS *m/z* (rel intensity, 70 eV) 245.15 (M^+, 3.3), 217.05 (15.8), 216.05 (100), 100.55 (6.1), 86.05 (6.2); $[\alpha]^{20}_D$ −5.1° (*c* 1.0, MeOH).

(*S*)-(−)-3-(3-Allylphenyl)-1-propylpiperidine (24) (Scheme 3). This compound was prepared as described for **19** from **6** (910 mg, 2.59 mmol) and allyltributyltin (900 mg, 2.72 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 19:1 (v/v)) afforded 333 mg (53%) of **24** as two double-bond isomers according to GC-MS (**24a** + **24b**). MS *m/z* (rel intensity, 70 eV) 243.15 (M^+, 5.7), 215.1 (17.5), 214.1 (100), 149.0 (12.3), 129.0 (15.4), 86 (15.0).

(*S*)-(−)-1-Propyl-3-(3-propylphenyl)piperidine 25 (Scheme 3). Compound **24** (459 mg, 1.88 mmol) was dissolved in 25 mL of methanol. Solid ammonium formate (225 mg, 3.57 mmol) and Pd/C (30 mg) were added.[32] The resulting mixture was refluxed under a nitrogen atmosphere for 4 h. The mixture was filtered through a pad of Celite, and the solvent was evaporated *in vacuo*. The residue was redissolved in 15 mL of 10% Na_2CO_3. The water phase was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to dryness. The crude product was purified by flash chromatography (CH_2Cl_2:MeOH, 9:1 (v/v)), affording **25** (407 mg, 88%). The amine was converted into the hydrochloride salt and recrystallized from ethanol/isopropyl ether: mp 176–179 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (m, 6H), 1.4–2.2 (m, 10H), 2.4 (m, 2H), 2.6 (t, 2H), 2,95 (tt, 1H), 3.2 (m, 2H), 7.0–7.3 (m, 4H); MS *m/z* (rel intensity, 70 eV) 245.2 (M^+, 6.7), 217.1 (17.4), 216.1 (100), 117.0 (8.5), 70.1 (13.1); $[\alpha]^{20}_D$ −4.4° (*c* 1.0, MeOH).

(*S*)-(+)-3-Piperidin-3-ylbenzonitrile (26) (Scheme 4). A solution of **10** (3.93 g, 17.2 mmol) in 1,2-dichloroethane (50 mL) was cooled to 0 °C. Then α-chloroethyl chloroformate (3.69 g, 25.8 mmol) in 1,2-dichloroethane (30 mL) was added dropwise at 0 °C.[37] The reaction mixture was then brought to reflux and followed by GLC. Five portions (1 mL) of α-chloroethyl chloroformate were added during a period of 2 days, and the conversion was complete (GLC) after 3 days. The heating was interrupted, and the volatiles were evaporated *in vacuo*. The residue was triturated with methanol (150 mL) and refluxed for 2.5 h. The solvent was evaporated to afford **26**·HCl as light-brown crystals. The product was chromatographed on a silica column with CH_2Cl_2:MeOH (25:1 (v/v), the methanol was saturated with NH_3(g)) as eluent. Collection of the fractions containing pure product and evaporation of the solvent afforded pure **26** (2.7 g, 84%). A small sample was converted to the fumarate salt and recrystallized in ethanol/isopropyl ether: m.p 120–124 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.69 (dq, J = 12.7, 3.2 Hz, 1H), 2.13 (m, 3H), 2.94 (m, 2H), 3.37 (m, 1H), 3.58 (m, 2H), 7.43–7.6 (m, 4H); MS *m/z* (rel intensity, 70 eV) 186.05 (M^+, 48.6), 185.05 (28.1), 129.00 (60.8), 128.00 (27.1), 57.00 (100), 56.00 (55.8); $[\alpha]^{20}_D$ +1.7° (*c* 1.0, MeOH).

(*S*)-(+)-3-(1-Methylpiperidin-3-yl)benzonitrile (27) (Schemes 4). Compound **26** (500 mg, 2.69 mmol), glacial acetic acid (161 mg, 2.69 mmol), and paraformaldehyde (88.7 mg, 2.96 mmol) were mixed in 1,2-dichloroethane (30 mL). Sodium triacetoxyborohydride (854 mg, 4.03 mmol) was added to the solution, and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 5 h (GLC analysis indicated a complete reaction).[38] The reaction was quenched with saturated aqueous $NaHCO_3$, and the product was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was evaporated to afford **27** as a oily residue. The product was chromatographed on a silica column with CH_2Cl_2:MeOH (9:1 (v/v)) as eluent. Collection of the fractions containing pure product and evaporation of the solvent afforded pure **27** (481 mg, 89%). The amine was converted into the hydrochloride salt and recrystallized from ethanol/isopropyl ether: mp 210–212 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.68 (qd, J_1 = 12.6, 2.8 Hz, 1H), 2.10 (t, J = 16.7 Hz, 2H), 2.46 (m, 1H), 2.73–2.9 (m, 5H), 3.5–3.72 (m, 3H), 7.28–7.61 (m, 4H); MS *m/z* (rel intensity, 70 eV) 200.05 (M^+, 33.1), 199.05 (22.0), 128.95 (16.4), 71.05 (31.4), 57.95 (100); $[\alpha]^{20}_D$ +2.5° (*c* 1.0, methanol).

(*S*)-(−)-3-(1-Ethylpiperidin-3-yl)benzonitrile (28) (Schemes 4). This compound was prepared as described for **27** from **26** (363 mg, 1.95 mmol) and acetaldehyde (98.7 mg, 2.15 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 12:1 (v/v)) afforded 380 mg (91%) of pure **28** as an oil. The amine was converted to the hydrochloride salt with HCl-saturated ethanol and recrystallized from ethanol/isopropyl ether: mp 192–194 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.50 (t, J = 7.3 Hz, 3H), 1.68 (qd, J = 12.9, 3.4 Hz, 1H), 2.10 (qt, J = 13.0 Hz, 2H), 2.49 (m, 1H), 2.70 (q, J = 11.5 Hz, 2H), 3.13 (q, J = 7.3 Hz, 2H), 3.54–3.73 (m, 3H), 7.45–7.60 (m, 4H); MS *m/z* (rel intensity, 70 eV) 214.15 (M^+, 16.3), 199.15 (100), 115.95 (13.7), 72.05 (43.8), 57.05 (47.4); $[\alpha]^{20}_D$ −10.3° (*c* 1.0, methanol).

(*S*)-(−)-3-(1-Isopropylpiperidin-3-yl)benzonitrile (29) (Scheme 4). A suspension of **26** (500 mg, 2.69 mmol) and ground K_2CO_3 (400 mg) was stirred in CH_3CN (30 mL) at room temperature. A solution of 2-bromopropane (331 mg, 2.69 mmol) in CH_3CN (5 mL) was added dropwise. The mixture was stirred at 50 °C for 5 days, and 0.5 equiv of 2-bromopropane was added each day. The reaction mixture was filtered, and the volatiles were evaporated *in vacuo*. The oily residue was chromatographed on a silica column with MeOH:CH_2Cl_2 (1:25 (v/v)) as eluent. Collection of the fractions containing pure product and evaporation of the solvent afforded pure **29** (570 mg, 93%). The amine was converted into the hydrochloride and recrystallized from ethanol/isopropyl ether: mp 185–186 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.1 (dd, J = 6.6 Hz, 6H), 1.46 (qd, J = 12.3, 4.3 Hz, 1H), 1.7–2.0 (m, 3H), 2.2 (m, 2H), 2.8–3.0 (m, 4H), 7.4–7.6 (m, 4H); MS *m/z* (rel intensity, 70 eV) 228.1 (M^+, 4.8), 214.1 (15.2), 213.1 (100), 129.05 (5.4), 116.05 (9.8), 70.95 (4.5); $[\alpha]^{20}_D$ −14.6° (*c* 1.0, MeOH).

(S)-(+)-3-(1-Allylpiperidin-3-yl)benzonitrile (30) (Scheme 4). This compound was prepared as described for **29** from **26** (173 mg, 0.93 mmol) and allyl bromide (118 mg, 0.98 mmol, added dropwise over a period of 3 h). The reaction mixture was stirred at room temperature overnight. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 19:1 (v/v)) afforded 112 mg (64%) of pure **30** as an oil. The amine was converted to the hydrochloride salt with HCl-saturated ethanol and recrystallized from ethanol/isopropyl ether: mp 183–185 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.67 (qd, J = 12.8, 2.7 Hz, 1H), 2.09 (t, J = 16.7 Hz, 2H), 2.46 (m, 1H), 2.73 (m, 2H), 3.5–3.73 (m, 5H), 5.48–5.57 (m, 2H), 6.21 (m, 1H), 7.44–7.6 (m, 4H); MS *m/z* (rel intensity, 70 eV) 226.05 (M^+, 39.8), 225.05 (34.2), 199.05 (37.9), 84.00 (100), 82.00 (42.1); $[\alpha]^{20}_D$ +0.2° (*c* 1.0, MeOH).

(S)-(−)-3-(1-Prop-2-ynylpiperidin-3-yl)benzonitrile (31) (Scheme 4). This compound was prepared as described for **29** from **26** (363 mg, 1.95 mmol) and propargyl bromide (237 mg, 1.99 mmol). The reaction mixture was stirred at room temperature for 1 h. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 25:1 (v/v)) afforded 302 mg (69%) of pure **31** as an oil. The amine was converted to the hydrochloride salt with HCl-saturated ethanol and recrystallized from ethanol/isopropyl ether: mp 195–196 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.45 (qd, J = 12.2, 4.1 Hz, 1H), 1.65–2.0 (m, 3H), 2.3 (m, 3H), 2.9 (m, 3H), 3.35 (d, J = 2.5 Hz, 2H), 7.44–7.6 (m, 4H); MS *m/z* (rel intensity, 70 eV) 224.05 (M^+, 82.4), 223.05 (95.3), 129.05 (79.6), 116.00 (54.9), 94.00 (100); $[\alpha]^{20}_D$ −7.6° (*c* 1.0, MeOH).

(S)-(−)-3-(1-Butylpiperidin-3-yl)benzonitrile (32) (Scheme 4). This compound was prepared as described for **29** from **26** (250 mg, 1.34 mmol) and 1-bromobutane (193 mg, 1.41 mmol). The reaction mixture was refluxed for 2 days. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 25:1 (v/v)) afforded 246 mg (76%) of pure **32** as an oil. The amine was converted to the fumarate salt and crystallization from ethanol/isopropyl ether yielded a gum: mp 117–119 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H), 1.2–1.6 (m, 5H), 1.65–2.0 (m, 5H), 2.35 (m, 2H), 2.87 (tt, 1H), 2.96 (br, d, 2H), 7.37–7.53 (m, 4H); MS *m/z* (rel intensity, 70 eV) 242.15 (M^+, 2.6), 200.1 (14.8), 199.1 (100), 156.0 (5.7), 129.0 (5.5), 116.0 (7.5); $[\alpha]^{20}_D$ −9.6° (*c* 1.0, MeOH).

(S)-(−)-3-(1-*sec*-Butylpiperidin-3-yl)benzonitrile (33) (Scheme 4). This compound was prepared as described for **29** from **26** (0.7 g, 3.76 mmol) and 2-iodobutane (0.7 g, 3.8 mmol). The mixture was stirred at 40 °C for 30 h. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 19:1 (v/v)) afforded 700 mg (77%) of pure **33** as an oil. The amine was converted into the fumarate salt and recrystallized from ethanol/isopropyl ether: mp 153–157 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H), 1.0 (dd, 3H), 1.2–2.0 (m, 6H), 2.1–2.4 (m, 2H), 2.5 (m, 1H), 2.8 (m, 3H), 7.37–7.53 (m, 4H); MS *m/z* (rel intensity, 70 eV) 242.25 (M^+, 1.1), 227.25 (8.2), 214.25 (15.9), 213.25 (100), 129.1 (5.0), 116.1 (10.6); $[\alpha]^{20}_D$ −19.9° (*c* 1.0, MeOH).

(S)-(−)-3-[1-(Cyclopropylmethyl)piperidin-3-yl]benzonitrile (34) (Scheme 4). This compound was prepared as described for **29** from **26** (500 mg, 2.69 mmol) and (bromomethyl)cyclopropane (399 mg, 2.95 mmol). The reaction mixture was stirred at 40 °C for 8 h. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 25:1 (v/v)) afforded 516 mg (80%) of pure **34** as an oil. The amine was converted to the fumarate salt and recrystallized from ethanol/isopropyl ether: mp 139–142 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (m, 2H), 0.54 (m, 2H), 0.90 (m, 1H), 1.48 (dq, J = 12.2 Hz, 4.6 Hz, 1H), 1.75–1.85 (m, 2H), 1.92–2.09 (m, 3H), 2.32 (d, J = 6.6 Hz, 2H), 2.92 (tt, J = 11.4, 3.6 Hz, 1H), 3.14 (br, d, 2H), 7.39–7.56 (m, 4H); MS *m/z* (rel intensity, 70 eV) 240.15 (M^+, 20.1), 199.05 (94.7), 129.00 (66.8), 116.0 (34.7), 98.0 (49.5), 96.0 (49.5), 57.0 (74.4), 55.0 (100); $[\alpha]^{20}_D$ −19.1° (*c* 1.0, MeOH).

(S)-(−)-3-(1-Phenethylpiperidin-3-yl)benzonitrile (35) (Scheme 4). This compound was prepared as described for **29** from **26** (167 mg, 0.9 mmol) and 2-phenylethyl bromide (182 mg, 0.99 mmol). The reaction mixture was stirred at 50 °C overnight. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 19:1 (v/v)) afforded 211 mg (81%) of pure **35** as an oil. The amine was converted to the fumarate salt and recrystallized from ethanol/isopropyl ether: mp 185–187 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.44 (dq, J = 12.5, 4.45 Hz, 1H), 1.71–2.12 (m, 5H), 2.66 (t, 2H), 2.8–3.07 (m, 5H), 7.17–7.54 (m, 9H); MS *m/z* (rel intensity, 70 eV) 290.12 (M^+, 0.1), 200.03 (17.47), 199.03 (100), 156.02 (4.37), 129.07 (3.22); $[\alpha]^{20}_D$ −6.6° (*c* 1.0, MeOH).

(S)-(−)-3-[1-(3-Phenylpropyl)piperidin-3-yl]benzonitrile (36) (Scheme 4). This compound was prepared as described for **29** from **26** (350 mg, 1.88 mmol) and 1-bromo-3-phenylpropane (237 mg, 1.99 mmol). The reaction mixture was refluxed for 4 h. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 30:1 (v/v)) afforded 410 mg (72%) of pure **36** as an oil. The amine was converted into the fumarate salt and recrystallized from 2-propanol/isopropyl ether: mp 158–159 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.44 (dq, J = 12.0, 4.41 Hz, 1H), 1.71–2.1 (m, 7H), 2.4 (m, 2H), 2.66 (m, 2H), 2.8–3.07 (m, 5H), 7.17–7.54 (m, 9H); MS *m/z* (rel intensity, 70 eV) 304.15 (M^+, 3.3), 200.1 (14.3), 199.1 (100), 116.0 (5.7), 91.0 (8.3); $[\alpha]^{20}_D$ −18.6° (*c* 1.0, MeOH).

(S)-(−)-3-[1-(2-Thiophene-3-ylethyl)piperidin-3-yl]benzonitrile (37) (Scheme 4). This compound was prepared as described for **29** from **26** (183 mg, 0.98 mmol) and 2-(thiene-2-yl)ethyl methanesulfonate (222 mg, 1.08 mmol). The reaction mixture was refluxed for 4 h. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 19:1 (v/v)) afforded 144 mg (60%) of pure **37** as an oil. The amine was converted to the fumarate salt and recrystallized from ethanol/isopropyl ether: mp 195–199 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.51 (dq, 1H), 1.73–2.19 (5H), 2.74 (m, 2H), 2.95 (tt, 1H), 3.05–3.11 (m, 4H), 6.86 (dd, 1H), 6.98 (dd, 1H), 7.17 (dd, 1H), 7.3–7.59 (m, 4H); MS *m/z* (rel intensity, 70 eV) 295.95 (M^+, 0), 200.05 (14.5), 199.05 (100), 156.0 (7.0), 129.0 (5.4), 116.0 (10.5); $[\alpha]^{20}_D$ −10.1° (*c* 1.0, MeOH).

(S)-(−)-3-[1-[3-(Dimethylamino)propyl]piperidin-3-yl]-benzonitrile (38) (Scheme 4). This compound was prepared as described for **29** from **26** (416 mg, 2.24 mmol) and 3-dimethylaminopropyl chloride hydrochloride (371 mg, 2.35 mmol). The reaction mixture was refluxed for 18 h. Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 3:1 (v/v)) afforded 230 mg (38%) of pure **38** as an oil. The amine was converted into the hydrochloride with HCl-saturated ethanol and recrystallized from methanol/isopropyl ether: mp 264–266 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.3 (dq, 1H), 1.5–1.9 (m, 7H), 2.1 (s, 6H), 2.15–2.35 (m, 4H), 2.75 (tt, 1H), 2.85 (m, 2H), 7.1–7.5 (m, 4H); MS *m/z* (rel intensity, 70 eV) 271.25 (M^+, 4.8), 226.15 (60.8), 211.15 (69.0), 199.15 (47.4), 197.15 (25.4), 110.05 (28.7), 86.05 (100); $[\alpha]^{20}_D$ −21.6° (*c* 1.0, MeOH).

(S)-(+)-Trifluoromethanesulfonic Acid 3-(1-Methylpiperidin-3-yl)phenyl Ester (39). This compound was prepared as described for **6** from (*S*)-3-(3-hydroxyphenyl)-*N*-methylpiperidine[52] (200 mg, 1.05 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 9:1 (v/v)) afforded 307 mg (91%) of pure **39** as an oil. The amine was converted into the hydrochloride with HCl-saturated ethanol, and crystallization from methanol/isopropyl ether yielded a gum: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.65 (qd, 1H), 2.05 (dt, 1H), 2.15 (m, 1H), 2.45 (m, 1H), 2.6–2.75 (m, 2H), 2.8 (s, 3H), 3.5–3.7 (m, 3H), 7.1–7.5 (m, 4H); MS *m/z* (rel intensity, 70 eV) 324.0 (M^+ + 1, 2.5), 323.0 (M^+, 14.0), 190.05 (42.0), 189.15 (11.5), 118.95 (5.8), 90.95 (14.6), 83.95 (10.3), 70.95 (36.4), 68.95 (16.9), 57.95 (100); $[\alpha]^{20}_D$ +1.3° (*c* 1.0, MeOH).

(S)-(−)-Trifluoromethanesulfonic Acid 3-(1-Ethylpiperidin-3-yl)phenyl Ester (40). This compound was prepared as described for **6** from (*S*)-3-(3-hydroxyphenyl)-*N*-ethylpiperidine[52] (200 mg, 0.97 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 9:1 (v/v)) afforded 289 mg (88%) of pure **40** as an oil. The amine was converted to the hydrochloride salt with HCl-saturated ethanol, and crystallization from ethanol/isopropyl ether yielded a gum: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.45 (t, 3H), 1.6 (qd, 1H), 2.0 (dt, 1H), 2.15 (m, 1H), 2.4–2.65 (m, 3H), 3.05 (q, 2H), 3.5–

3.75 (m, 3H), 7.1–7.3 (m, 2H), 7.35 (d, 1H), 7.45 (t, 1H); MS *m/z* (rel intensity, 70 eV) 338.0 ($M^+ + 1$, 2.8), 337.0 (M^+, 15.7), 323.0 (15.5), 322.0 (100), 204.05 (36.4), 203.05 (16.7), 189.05 (50.6), 90.95 (24.7); $[\alpha]^{20}_D$ −8.0° (*c* 1.0, MeOH).

(*S*)-(−)-Trifluoromethanesulfonic Acid 3-[1-(Phenylethyl)piperidin-3-yl]phenyl Ester (41). This compound was prepared as described for **6** from (*S*)-3-(3-hydroxyphenyl)-*N*-(2-phenylethyl)piperidine[52] (200 mg, 0.71 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 25:1 (v/v)) afforded 246 mg (84%) of pure **41** as an oil. The amine was converted to the fumarate salt and recrystallized in ethanol/isopropyl ether: mp 202–205 °C (fumarate); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.46 (dq, 1H), 1.7–2.0 (m, 3H), 2.1 (t, 2H), 2.66 (m, 2H), 2.8–3.2 (m, 5H), 7.17–7.54 (m, 9H); MS *m/z* (rel intensity, 70 eV) 323.05 (16.0), 322.05 (100, $M^+ - 91$), 189.10 (50.2), 188.20 (11.3), 105.00 (11.1), 91.00 (12.0); $[\alpha]^{20}_D$ −3.0° (*c* 1.0, base, MeOH).

Trifluoromethanesulfonic Acid 2-(1-Propylpiperidin-3-yl)phenyl Ester (42). This compound was prepared as described for **6** from 3-(2-hydroxyphenyl)-1-propylpiperidine[51] (200 mg, 0.91 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 25:1 (v/v)) afforded 271 mg (85%) of pure **42** as an oil. The amine was converted into the hydrochloride with HCl-saturated ethanol and recrystallized from ethanol/isopropyl ether: mp 202–204 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.4–2.4 (m, 10H), 2.9 (m, 2H), 3.2 (m, 1H), 7.25–7.5 (m, 4H); MS *m/z* (rel intensity, 70 eV) 351.05 (M^+, 4.1), 322.05 (100), 218.05 (21.6), 189.10 (48.8), 147.00 (31.3), 107.00 (17.1).

Trifluoromethanesulfonic Acid 4-(1-Propylpiperidin-3-yl)phenyl Ester (43). This compound was prepared as described for **6** from 3-(4-hydroxyphenyl)-1-propylpiperidine[51] (210 mg, 0.96 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 9:1 (v/v)) afforded 309 mg (92%) of pure **43** as an oil. The amine was converted into the hydrochloride with HCl-saturated ethanol and recrystallized from ethanol/isopropyl ether: mp 166–170 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.65 (qd, 1H), 1.8–3.0 (m, 9H), 3.5 (m, 3H), 7.2 (d, 2H), 7.3 (d, 2H); MS *m/z* (rel intensity, 70 eV) 351.15 (M^+, 4.1), 323.1 (18.0), 322.05 (100), 189.15 (19.6), 86.15 (33.1), 69.00 (12.6).

(*S*)-(−)-Trifluoromethanesulfonic Acid 5-(1-Propylpiperidin-3-yl)-2-[[(trifluoromethyl)sulfonyl]oxy]phenyl Ester (44). This compound was prepared as described for **6** from (*S*)-(−)-3-(3,4-dihydroxyphenyl)-1-propylpiperidine[74] (340 mg, 1.08 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 12:1 (v/v)) afforded 430 mg (80%) of pure **44** as an oil. The amine was converted into the hydrochloride with HCl-saturated ethanol and recrystallized from ethanol/isopropyl ether: mp 138–140 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.3–2.1 (m, 8H), 2.4 (m, 2H), 2.9 (m, 3H), 7.4 (m, 3H); MS *m/z* (rel intensity, 70 eV) 499.1 (M^+, 2.8), 472.05 (11.2), 471.1 (17.5), 470.1 (100), 204.2 (20.5), 176.15 (10.4); $[\alpha]^{20}_D$ −6.9° (*c* 1.0, MeOH).

***cis*-(±)-Trifluoromethanesulfonic Acid 4-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolin-7-yl Ester (45).** This compound was prepared as described for **6** from *cis*-(±)-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline[61] (235 mg, 0.91 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 19:1 (v/v)) afforded 300 mg (87%) of pure **45** as an oil. The amine was converted into the hydrochloride with HCl-saturated ethanol and recrystallized from ethanol/isopropyl ether: mp 198–204 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.5–2.0 (m, 8H), 2.4–2.7 (m, 5H), 3.0–3.2 (m, 3H), 7.05 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.1–7.2 (m, 2H); MS *m/z* (rel intensity, 70 eV) 377.2 (M^+, 7.2), 349.05 (18.2), 348.05 (100), 244.2 (18.4), 215.1 (20.3).

***trans*-(±)-Trifluoromethanesulfonic Acid 4-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolin-7-yl Ester (46).** This compound was prepared as described for **6** from *trans*-(±)-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline[61] (473 mg, 1.93 mmol). Purification of the crude reaction mixture by flash chromatography (CH_2Cl_2:MeOH, 19:1 (v/v)) afforded 660 mg (91%) of pure **46** as an oil. The amine was converted into the hydrochloride salt with HCl-saturated ethanol and recrystallized from ethanol/diethyl ether: mp 239–241 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 3H), 1.25 (m, 1H), 1.4–1.9 (m, 5H), 2.15 (dt, *J* = 10.8, 2.4 Hz, 1H), 2.25–3.1 (m, 9H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.2 (t, *J* = 8.0 Hz, 1H), 7.3 (d, *J* = 8.0 Hz, 1H); MS *m/z* (rel intensity, 70 eV) 377.2 (M^+, 5.7), 349.05 (18.5), 348.05 (100), 244.2 (8.6), 215.1 (25.7).

***trans*-(±)-Trifluoromethanesulfonic Acid 3-Propyl-2,3,-3a,4,5,9b-hexahydro-1*H*-benz[*e*]indol-6-yl Ester (47).** A solution of *trans*-(±)-3-propyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indol-6-ol[39] (134 mg, 0.5 mmol) and pyridine (10 mL) in 45 mL of methylene chloride was cooled to 0–5 °C, and trifluoromethanesulfonic anhydride was added slowly over a period of 5 min. The resulting brown solution was stirred at room temperature for 2 h. The reaction was quenched with aqueous saturated sodium bicarbonate and extracted with ethyl acetate (2 × 1 L). The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a brown oil. The oil was purified on 400 g of silica gel, eluting with hexane:acetone (4:1 (v/v)) and collecting 40 mL fractions. Fractions homogeneous by TLC were collected and concentrated *in vacuo* to give pure **47** as a light-yellow oil (160 mg, 88.9%). The amine was converted into the hydrochloride salt with HCl-saturated methanol and recrystallized from EtOAc/hexane: mp 196–197 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06 (t, *J* = 7.3 Hz, 3H), 1.70–4.24 (m, 14 H), 7.10–7.30 (m, 3H).

***trans*-(±)-Trifluoromethanesulfonic Acid 3-Allyl-2,3,-3a,4,5,9b-hexahydro-1*H*-benz[*e*]indol-6-yl Ester (48).** This compound was prepared as described for **47** from *trans*-(±)-3-allyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indol-6-ol[39] (425 mg, 1.6 mmol), and the reaction was run in neat pyridine. Purification of the crude reaction mixture by liquid chromatography (hexane:acetone, 4:1 (v/v)) afforded 420 mg (72%) of pure **48** as an oil. The amine was converted into the hydrochloride with HCl-saturated methanol and recrystallized from EtOAc/hexane: mp 174–175 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.88–4.14 (m, 12H), 5.5–6.24 (m, 3H), 7.03–7.34 (m, 3H); MS *m/z* (rel intensity, 70 eV) 361 (M^+), other ions at *m/z* 334, 228, 200.

***cis*-(+)-Trifluoromethanesulfonic Acid 3-Allyl-2,3-(3a*S*),4,5(9b*R*)-hexahydro-1*H*-benz[*e*]indol-6-yl Ester (49).** This compound was prepared as described for **47** from *cis*-(+)-3-allyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indol-6-ol[39] (1.85 g, 8.0 mmol). Purification of the crude reaction mixture by liquid chromatography (hexane:acetone, 9:1 (v/v)) afforded 2.5 g (87%) of pure **49** as an oil. The amine was converted into the hydrochloride with HCl-saturated methanol and recrystallized from EtOAc/hexane: mp 144–145 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.6–3.54 (m, 12H), 5.1–6.05 (m, 3 H), 7.0–7.2 (m, 3H); $[\alpha]_D^{25}$ +6° (*c* 0.72, MeOH).

***cis*-(−)-Trifluoromethanesulfonic Acid 3-Allyl-2,3-(3a*R*),4,5(9b*S*)-hexahydro-1*H*-benz[*e*]indol-6-yl Ester (50) (Scheme 5).** This compound was prepared as described for **47** from *cis*-(−)-3-allyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indol-6-ol[39] (1.72 g, 7.5 mmol). Purification of the crude reaction mixture by flash chromatography (hexane:acetone, 9:1 (v/v)) afforded 1.83 g (68%) of pure **50** as an oil. The amine was converted into the hydrochloride with HCl-saturated methanol and recrystallized from EtOAc/hexane: mp 144–145 °C; $[\alpha]_D^{25}$ −9° (*c* 0.72, MeOH).

***cis*-(−)-3-Allyl-2,3(3a*R*),4,5(9b*S*)-hexahydro-1*H*-benz[*e*]-indole-6-carboxylic Acid Methyl Ester (51) (Scheme 5).** This compound was prepared as described for **7** from compound **50** (1.8 g, 5 mmol). Purification of the crude reaction mixture by flash chromatography (hexane:acetone, 4:1 (v/v)) afforded 0.7 g (52%) of pure **51** as an oil: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.58–3.52 (m, 12H), 3.88 (s, 3H), 5.05–6.03 (m, 3 H), 7.17 (t, *J* = 8 Hz, 1H), 7.27, (d, *J* = 8 Hz, 1H), 7.63, (d, *J* = 8 Hz, 1H).

***cis*-(−)-3-Allyl-2,3(3a*R*),4,5(9b*S*)-hexahydro-1*H*-benz[*e*]-indole-6-carboxylic Acid Amide (52) (Scheme 5).** A solution of methyl ester **51** (0.7 g, 2.6 mmol), 3 N NaOH (1.3 mL), and methanol (5.2 mL) was refluxed overnight. TLC analysis showed no starting material remaining. The mixture was neutralized with 6 N HCl (to pH 5) and concentrated to dryness using methanol and toluene. A light yellow solid as

a free acid was recovered. A solution of this solid in DMF (20 mL) and triethylamine (0.54 mL, 3.9 mmol) was flushed with ammonia gas for 10 min at 0 °C and treated with DEPC (0.6 mL, 3.9 mmol). Ammonia gas was bubbled through the solution overnight at room temperature. The reaction mixture was concentrated *in vacuo* to a solid and purified by liquid chromatography on 200 g of silica gel, eluting first with 500 mL of CH_2Cl_2 followed by CH_2Cl_2:MeOH (9:1, v/v) and collecting 40 mL fractions. Homogeneous fractions were combined and concentrated to yield a white solid (0.2 g, 30%). The solid was recrystallized from hexane/acetone: mp 170–172 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.6–3.6 (m, 12H), 5.1–6.05 (m, 3 H), 7.16–7.27 (m, 3H); $[\alpha]^{25}_D$ −56° (*c* 0.41, MeOH).

***cis*-(−)-3-Allyl-2,3(3a*R*),4,5(9b*S*)-hexahydro-1*H*-benz[*e*]-indole-6-carbonitrile (53) (Scheme 5).** This compound was prepared as described for **10** from compound **52** (109 mg, 0.42 mmol) and $POCl_3$ (0.2 mL, 2.1 mmol). Purification of the crude reaction mixture by liquid chromatography (hexane:acetone, 4:1 (v/v)) afforded 93 mg (92%) of pure **53** as an oil. The amine was converted into the hydrochloride salt with HCl-saturated methanol and recrystallized from EtOAc/methanol: mp 242–243 °C (HCl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.62–4.14 (m, 12H), 5.5–6.42 (m, 3H), 7.26–7.37 (m, 2H), 7.55 (d, J = 7.5 Hz, 1H); $[\alpha]^{25}_D$ −30.8° (*c* 0.5, MeOH).

Pharmacology. Animals. Animals used in the biochemical and motor activity experiments were male rats of the Sprague–Dawley strain (Bekay, Sollentuna, Sweden), weighing 200–300 g. The rats were kept 5/cage with free access to water and food at least 1 week from arrival until used in the experiments. The animals treated orally with drug were starved 18 h before the experiment.

Drugs. All substances to be tested were dissolved in physiological (0.9%) saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose. Injection volumes were 5 or 10 mL/kg, and all solutions had neutral pH values (except for the solutions of reserpine).

Biochemistry (Biochemically Monitored DA and 5-HT Receptor Agonist or Antagonist Activity). The concept of the biochemical screening method is that a DA or 5-HT receptor agonist stimulates the corresponding receptor and through regulatory feedback systems induces a decrease in tyrosine or tryptophan hydroxylase activity, respectively, and a subsequent reduction in the synthesis rate of DA and 5-HT. DOPA or 5-HTP formation, as determined after *in vivo* inhibition of the aromatic L-amino acid decarboxylase with NSD 1015 ((3-hydroxybenzyl)hydrazine hydrochloride), is taken as indirect measures of DA and 5-HT synthesis rates, respectively.[48,75] The biochemical experiments and the determinations of DOPA and 5-HTP by means of HPLC with electrochemical detection were performed according to a modification of a previously described method.[76,77] Receptor antagonist effects are seen as increases in the synthesis rate of neurotransmitter. This is a result of inhibition of the feedback down regulation of transmitter synthesis. The effects on DOPA accumulation are expressed as percent of controls, which is DOPA striatum = 1350 ± 25 ng/g, mean ± SEM, n = 77 (Tables 2 and 5). In the experiments with habituated rats, no NSD 1015 was administered and the animals were killed 1 h after drug administration. The brains were dissected, and the levels of DOPAC (control levels: striatum 1022 ± 38 ng/g, mean ± SEM, n = 24) were assayed by means of HPLC with electrochemical detection.[78] The levels are expressed as percent of controls (DOPAC, Tables 2 and 5).

Motor Activity. Reserpine-Pretreated Animals. The motor activity was measured by means of photocell recordings (M/P 40 Fc electronic motility meter, Motron Products, Stockholm) as previously described.[75] Eighteen hours prior to the motility testing (carried out between 9 a.m. and 1 p.m.), the rats were injected with reserpine (5 mg/kg sc) in the neck region. On the day of experiment, the different test compounds were administered subcutaneously in the neck region (n = 4). Immediately after drug administration, the rats were put into the motility meters (1 rat/cage). Motor activity was then followed and recorded for the subsequent 30 min (reserpine control values 3 ± 1 counts/30 min, mean ± SEM, n = 13, Tables 2 and 5). Observations of gross behavior were made throughout the activity sessions through semitransparent mirrors.

Nonpretreated Animals. The motor activity was measured as described for reserpine-pretreated animals. The different test compounds were administered subcutaneously in the flank. Immediately after drug administration, the rats were placed in the test cages (1 rat/cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 30 min (Table 2). Observations of gross behavior were made throughout the activity sessions through semitransparent mirrors. Control levels were 229 ± 24 counts/30 min (means ± SEM, n = 4).

Nonpretreated Habituated Animals. These experiments were performed as described above, but the animals were habituated in the test cages 1 h before the injection of the test compound or saline (controls). The habituation resulted in a locomotor activity of about 10% of that seen in nonpretreated animals. The locomotor activity after the test compound was then recorded for 60 min (Tables 2 and 5). Control levels were 44 ± 15 counts/60 min (means ± SEM, n = 4).

Microdialysis. Following the placement of a small burr hole in the appropriate location on the cranium over the corpus striatum (A 1, L 2.6, and D 6), male Sprague–Dawely rats were stereotaxically implanted with a flexible plastic dialysis probe.[57] The rats were then allowed to recover for 48 h before the experiment started. After connection to a perfusion pump, delivering a Ringers solution containing in mmol/L: NaCl 140, $CaCl_2$ 1.2, KCl 3.0, $MgCl_2$ 1.0, and ascorbic acid 0.04, the rats were placed in an open cage and allowed to move freely within its domains. The dialysate contents of DA and its metabolites were analyzed on a HPLC-EC system, allowing 5 min runs for each sample using a sample splitting technique.[79] Drugs were dissolved in physiological saline and injected sc in the flank. The effect of the drugs was studied during 3 h. After the experiment, the rats were decapitated and the brains taken out and frozen on a block of dry ice. The location of the probes was controlled by means of a Leitz freezing microtome (Table 3).

Receptor Binding. IC_{50} values were estimated from a nonlinear single-site fit to data obtained from competition binding experiments run in single, duplicate, or triplicate. Radio receptor binding studies with [^{3}H]-8-OH-DPAT (5-HT_{1A} agonist, 143–158 Ci/mmol, New England Nuclear, Boston, MA), and [^{3}H]spiperone (D_2 antagonist, 21–24 Ci/mmol, New England Nuclear, Boston, MA) were performed using rat striatal membrane preparations as previously described.[80,81]

Radioligands used in cloned mammalian receptors expressed in CHO-K1 cells[82,83] were [^{3}H]U-86170 (62 Ci/mmol, 2 nM)[84] and [^{3}H]spiperone (107 Ci/mmol, 0.5 nM) for D_2 dopamine and [^{3}H]spiperone (107 Ci/mmol, 0.6 nM) for D_3 dopamine receptors. The buffer used was 20 mM HEPES and 10 mM $MgSO_4$, pH 7.4, for D_2 dopamine receptors. The buffer used for D_3 dopamine receptors was 20 mM HEPES, 10 mM $MgCl_2$, 150 mM NaCl, and 1 mM EDTA, pH 7.4. Incubation of the 0.9 mL binding mixtures was for 1 h at room temperature. Reactions were stopped by vacuum filtration. Counting was with a 1205 betaplate (Wallac) using MeltiLex B/HS (Wallac) as scintillant. Dissociation constants (K_i) were calculated with the Cheng and Prushoff equation.[85] The data in Tables 1 and 4 are in nM ± SEM.

***In Vivo* Di-Pr-5,6-ADTN Displacement and Motor Activity Measurements.** The procedures applied in these experiments are essentially the same as described by Feenstra et al.[41] but altered according to Carlsson and Löfberg.[42] The rats were injected with Di-Pr-5,6-ADTN (0.25 μmol/kg sc); 60 min later, the test drug was injected. After 5 min, the rats were placed in the motility meter boxes. The locomotor activity was recorded for 30 min. After an additional 5 min, the rats were killed by decapitation and their brains rapidly taken out. The striatum and cerebellum were dissected for further analysis of their content of Di-Pr-5,6-ADTN and DOPAC. The "specific" binding to striatal binding sites was calculated by subtracting the Di-Pr-5,6-ADTN content of the

cerebellum from that of the striatum. The motility measurements were carried out using a set of eight photocell animal motility meters (digiscan activity monitor RXYZM(16)TAO, Omnitech Electronics, Inc., Columbus, OH). The motility meters were kept in sound- and light-proof boxes equipped with semitransparent mirrors allowing observation of the animals during the course of the experiments. The data are presented in Table 3.

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Supplementary Material Available: List of ^{13}C-NMR data and C, H, and N analyses (7 pages). Ordering information is given on any current masthead page.

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