Structure–Activity Relationships in the 8-Amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole Ring System. 1. Effects of Substituents in the Aromatic System on Serotonin and Dopamine Receptor Subtypes

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Received October 17, 1994®

A series of 1-, 3-, and 4-substituted analogs to the potent 5-HT_{1A} agonist 8-(dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (**5**) were prepared and tested *in vitro* at 5-HT_{1A}, 5-$HT_{1D\alpha}$, 5-$HT_{1D\beta}$, D_2, and D_3 receptors and *in vivo* for agonist activity in the 5-HTP and DOPA accumulation assays in reserpine-pretreated rats. Some of the compounds were resolved. The substituents used in the 1-position were chosen from a principal component analysis (PCA) plot constructed from both tabulated variables and variables calculated by semiempirical methods (PM3) and molecular mechanics software (MMX). Among the analogs prepared, some, *e.g.*, compound **21**, were equipotent to compound **5** with respect to 5-HT_{1A} effects. All compounds were more or less selective for the 5-HT_{1A} receptor, but many of the compounds displayed higher affinities for 5-$HT_{1D\alpha}$ than for 5-$HT_{1D\beta}$ receptors.

Introduction

In the past decade, several articles have been published in the serotonin 5-HT_{1A} area. This interest started with the discovery that 8-hydroxy-2-(dipropylamino)-1,2,3,4-tetrahydronaphthalene (8-OH-DPAT, **1a**) showed potent agonistic activity in the serotonergic systems of the brain, with a high selectivity vs catecholaminergic systems.[1,2] 8-OH-DPAT (**1a**) was later found to act directly on a subtype of the 5-HT receptors, the 5-HT_{1A} receptor.[3,4] Since an increasing 5-HT transmission is thought to be beneficial for treating conditions like anxiety and depression (cf. treatment with reuptake inhibitors), it has been suggested that directly acting 5-HT_{1A} agonists may be applied in the same clinical areas. Buspirone **2**, a partial 5-HT_{1A} agonist, has found its place in the clinic as an alternative to the traditional treatment of anxiety and depression.[3–6]

In a series of articles, the tricyclic ring systems 8-(dialkylamino)-6,7,8,9-tetrahydrobenz[*e*]- and -[*g*]indoles were examined for their serotonergic activity.[7–9] This was initiated by the finding by Wikström *et al.*[8] that the unsubstituted 8-(dimethylamino)-6,7,8,9-tetrahydrobenz[*e*]indole (**3**) displayed serotonergic activity at 5-HT_{1A} receptors, beside its previously reported dopaminergic activity.[10] A subsequent paper from our group showed that the *N,N*-dipropyl analog of **3** (compound **4**) is a potent 5-HT_{1A} agonist, although not selective with regard to dopamine D_2 receptors.[9] In the same paper it was shown that introduction of a formyl group in the 1-position (compound **5** and enantiomers) altered the selectivity toward 5-HT_{1A} yielding one of the most potent 5-HT_{1A} agonists reported. This compound and its enantiomers were found to have superior (to 8-OH-DPAT, **1a**) oral bioavailability in rats. In a subsequent paper, Romero *et al.* showed that the corresponding 2-cyano compound **6** was equipotent to **5**, whereas the 2-carboxamide **7** was not as potent.[11] These findings resulted in a further analog investigation where the 1-cyano (**8**), 1-chloro (**9**), and 1,1,1-trifluoroethyl (**10**) analogs were tested and compared to compounds **5** and **6**.[7] The high potency of both cyano derivatives **6** and **8** and their enantiomers raised some questions concerning the drug–5-HT_{1A} receptor interaction. Compounds **9** and **10** were less potent. In the same article it was found that the isosteric (to **4**) 8-(dipropylamino)-6,7,8,9-tetrahydrobenz[*g*]indole (**11**) and analogs were inactive at 5-HT_{1A} receptors. Furthermore, the *N*-formylindoline **12**, which is easily superimposed on **5** and thus would seem to mimic **5**, was almost inactive at 5-HT_{1A} receptors.

This study is primarily a further investigation of the influence of different functional groups in the indole aromatic system of 8-(propylamino)-6,7,8,9-tetrahydrobenz[*e*]indoles on the affinity, *in vivo* potency, and selectivity for 5-HT_{1A} receptors vs D_2 receptors. The 1- and 2-positions of this ring system most likely correspond to 8-substituted aminotetralins in the drug–receptor interaction. Changes in these positions could affect 5-HT_{1A} receptor affinity, as has been noticed previously.[7,9,11] In a recent article by Liu *et al.*, the effect of various substituents in the 8-position of aminotetralins was investigated.[12] A number of potent

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® Abstract published in *Advance ACS Abstracts*, May 1, 1995.

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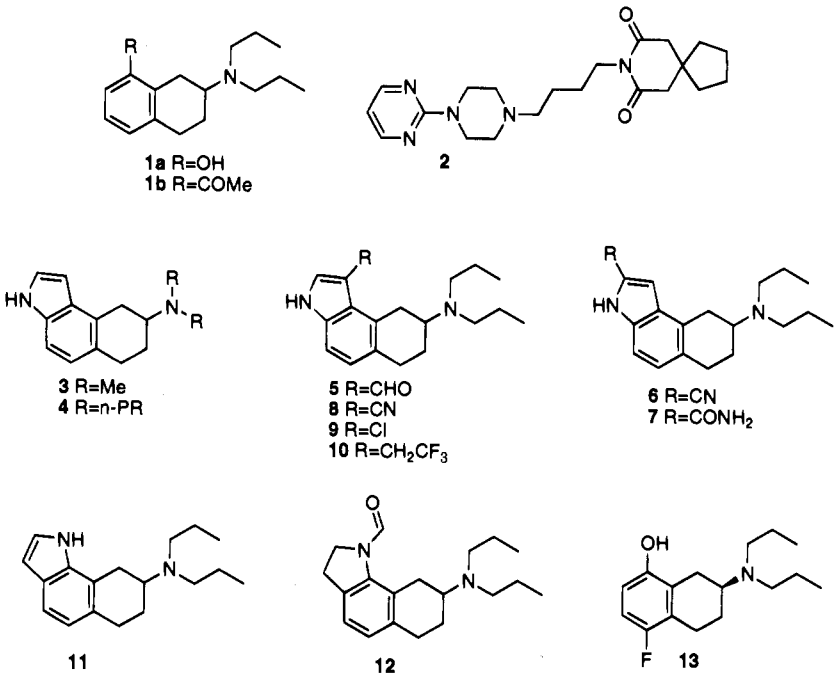


Figure 1. Structures discussed.

compounds were synthesized, including the acetyl derivative **1b.** Being analogs to the formyl group in **5,** it was of interest to introduce acyl functions in the 1-position of the pyrroloaminotetralin skeleton. These and the remaining substituents were chosen from a principal component analysis (PCA) map (Figure 2b).

The low affinities of compounds **11** and **12** raised questions concerning the importance of the indole NH moiety for the affinity for this type of compound, which would also be a subject of this investigation. In addition, we wanted to see if a small alteration in the 4-position (corresponds to 6-position in aminotetralins) would affect the *in vivo* and *in vitro* profile. Hillver *et al.* have shown that introduction of a fluorine in the 5-position of aminotetralins as in (*S*)-(−)-UH301 (*S*-(−)-**13**) may lead to 5-HT_{1A} antagonist activity.[13] However, alterations in the 5-position of aminotetralins may also give rise to dopaminergic effects. The 6-position (corresponding to 4-position of the 6,7,8,9-tetrahydrobenz-[*e*]indole system) seems to be less sensitive in that sense. We also wanted to see if the fluorine introduction would change the oral bioavailability. In the subsequent article, we will also investigate the effects of changes in the alkyl groups on the amino nitrogen.[14]

All analogs (and some of the precursors) were tested in most of the following *in vitro* binding models: 5-HT_{1A}, 5-$HT_{1D\alpha}$, 5-$HT_{1D\beta}$, D_2, and D_3. For consistency, some of the compounds from the previous publications were retested using CHO cells (previously rat brain homogenate). Binding to 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors was included in the investigation. These receptor subtypes seem to be the closest relatives to the 5-HT_{1A} subtype.[15] Selected compounds were tested for the effects on brain DOPA and 5-HTP synthesis rates in various parts of the rat brain.

Principal Component Analysis Mapping of Substituents

To extract as much structure−activity relationship (SAR) information as possible from a series of compounds, it is crucial to examine as much variability as possible in the physicochemical properties of the substituents to be used. Variables which are often used to obtain a physicochemical description of substituents are Hammet, Hansch, and Verloop parameters, molecular weight, etc. Such parameters can be collected from publications and handbook tables.[16-18] By using a principal component analysis (PCA), the systematic information of this multidimensional data set is extracted and reduced to a more easily interpreted two-dimensional map. This may aid the medicinal chemist in making the choice of substituents in a more systematic way. By choosing substituents from such a map with as much spread as possible, the probability of covering the greatest variety of physicochemical properties is enhanced. One problem with tabulated data of various substituents is that some variables are not available for all substituents. This renders some substituents that may be interesting from a synthetic, technical, or medicinal chemistry point of view impossible to implement in the PCA analysis. When it was decided to perform a QSAR investigation of this series, we found that many of the analogs already prepared were not well represented in the commonly used descriptors for substituents and tabulated data for many of these substituents were scarce. However, many variables, which carry equivalent information or more as tabulated data, can be calculated using readily accessible software. For this purpose, we performed molecular mechanics and semiempirical calculations of a large number of substituted benzenes, including those we wanted to use in our dataset. From the semiempirical calculations (PM3, Hyperchem[19]) the following variables were extracted, HOMO energies (E_{HOMO} and E_{HOMOn}), LUMO energies (E_{LUMO} and E_{LUMOn}), calculated dipole moment (μ_{calc}), isolated atomic energy (E_{IA}), bonding energy (E_{Bond}), electronic energy (E_{ELEC}), core−core interaction (E_{C-C}), and heat of formation (ΔH_f). From the molecular mechanics calculations, van der Waals surface areas, such as total surface area (A_{TOT}),

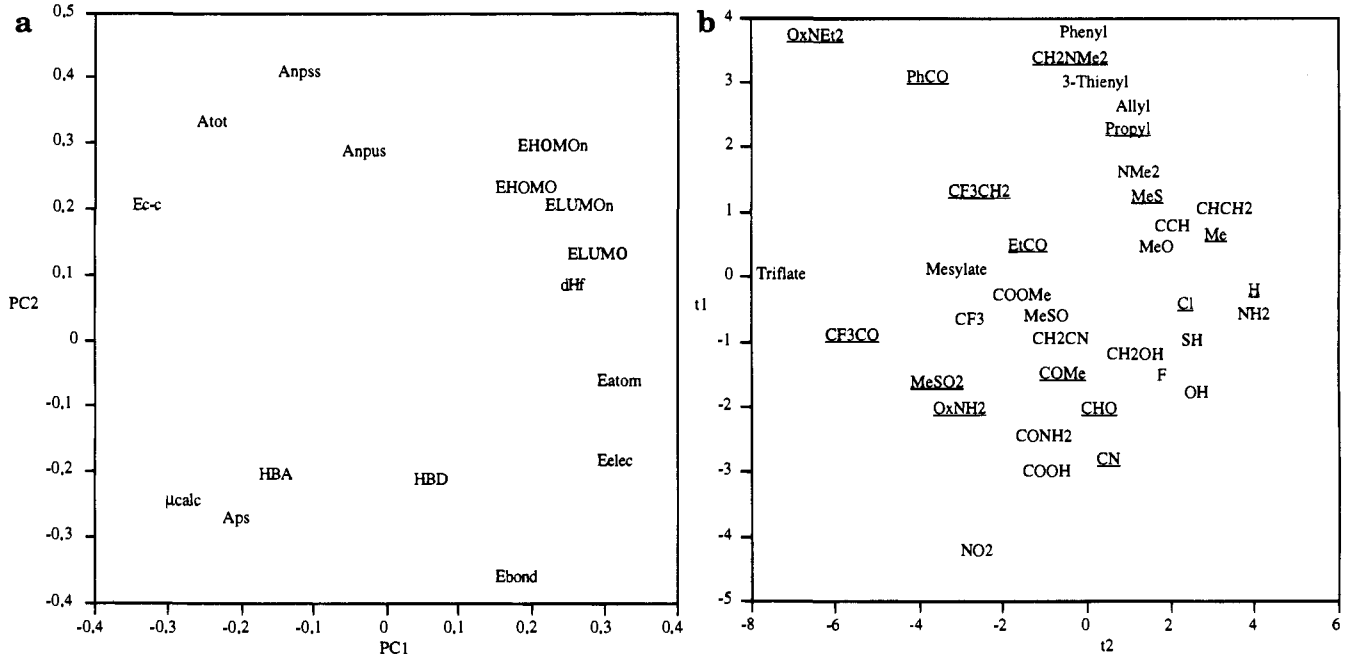


Figure 2. (a) Loading plot of the two first principal components (PC1 vs PC2) of the substituent describing variable dataset. (b) Score plot of various substituents. Substituent used are underlined. $OxNEt_2$ = oxalyl-*N*,*N*-diethylamide, $OxNH_2$ = oxalylamide.

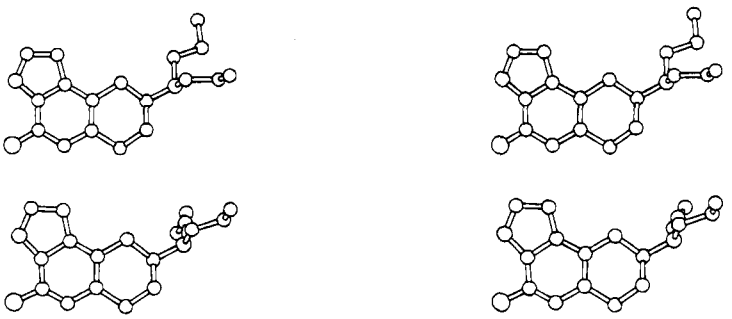


Figure 3. Stereodrawing of the X-ray crystal structure of compound (−)-*S*-**20**. Two slightly different conformations were found in each unit cell. The ditoluoyltartaric acid part of the structure has been omitted for clarity.

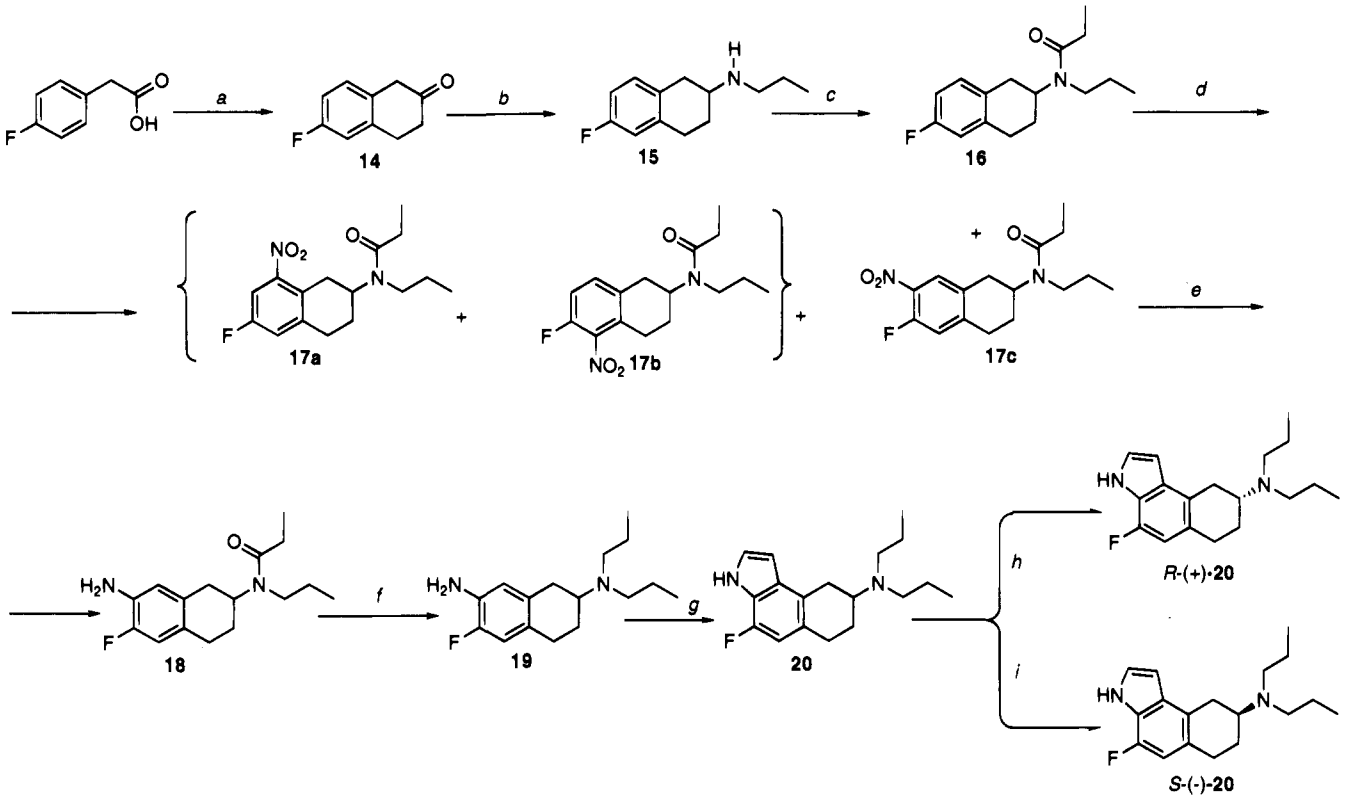
nonpolar saturated surface area (A_{NPSS}), nonpolar unsaturated surface area (A_{NPUS}), and polar surface area (A_{PS}), were derived. Variables (1/0) indicating hydrogen bond donor (HB_D) and acceptor (HB_A) abilities were also included. These variables were subjected to a principal component analysis. In this analysis six significant (by cross-validation, $R^2_{cv} = 0.68$) principal components were derived, which explained 90% of the total variance in the dataset. Figure 2a displays a loading plot of the two first principal components (describing 63% of the total variance). In Figure 2b, a score plot of the two first components is shown. The substituents chosen are underlined.

Chemistry

For the 4-fluoro compounds, a route similar to that previously described for the preparation of compounds **4** and **5** was outlined.[9,20] Thus, 6-fluoro-2-tetralone (**14**) was prepared from 4-fluorophenylacetic acid via Friedel–Crafts acylation of ethene and subsequent ring-closure alkylation.[21-23] Reductive amination with 1-propylamine gave **15**, which was treated with propionyl chloride to afford the amide **16**. Nitration of **16** gave three isomers (**17a–c**) where the major isomer **17c** was preferred. After purification on a silica gel column (eluted in the named order), **17c** was reduced in two steps, first by catalytic hydrogenation to compound **18** and then hydride reduction to the amine **19**. This material was subjected to Sandmeyer isatin synthesis[24,25] and hydride reduction to yield the fluorinated indole analog **20**. The enantiomers were prepared by diastereomeric salt resolution using ditoluoyltartaric acid.[9] The (−)-enantiomer was determined by X-ray analysis to have the *S*-configuration (Figure 3). Each crystal unit cell contains two *S*-(−)-**20** molecules with slightly different conformations of the *N*,*N*-dipropylamine moiety.

The formyl analogs (compounds **21**, *S*-(−)-**21**, and *R*-(+)-**21**) were made from compound **20** by the use of Vilsmeyer formylation.[26] The nitrile analog **22** was prepared as in ref 7 using chlorosulfonyl isocyanate. Vilsmeyer type propionylation of **20** afforded the 1-propionyl derivative **23**, which was further reduced with lithium aluminum hydride to yield the 1-*n*-propyl compound **24**. Compound **20** was methylated on the indole nitrogen with methyl iodide to yield **25**, which was 1-formylated into compound **26**. The 4-unsubstituted compounds were prepared as described in the following using **4** as starting material. Compound **4** was prepared either by the route of refs 9, 20, and 27 or by the route described by Lin *et al.*[27] The trifluoracetyl compound **27** was synthesized by acylation of **4** using

Scheme 1. Preparation of Compound **20** and Its Enantiomers[a]



[a] (a) 1. $SOCl_2$, CH_2Cl_2, reflux, 4 h, 2. $AlCl_3$, CH_2Cl_2, ethylene, −5−25 °C, 5 h; (b) *n*-$PrNH_2$, $NaCNBH_4$, HOAc, rt, 5 h; (c) EtCOCl, Et_3N, CH_2Cl_2, rt, 1.5 h; (d) HNO_3/H_2SO_4, $MeNO_2$, −5 °C, 30 min; (e) H_2 pressure, Pd/C, EtOH, 18 h; (f) $LiAlH_4$, ether, rt, 2 h; (g) 1. $Cl_3CCH(OH)_2$, H_2NOH·HCl, H_2O, reflux, 2. aq H_2SO_4, −10−80 °C, 3. $LiAlH_4$, ether, rt; (h) (+)-di-*p*-toluoyltartaric acid, EtOH; (i) (−)-di-*p*-toluoyltartaric acid, EtOH.

trifluoroacetic acid anhydride. Vilsmeyer acylation afforded the acetyl derivative **28** and the benzoyl derivative **29**. Treatment with oxalyl chloride followed by quenching with ammonia yielded the oxalyl amide derivative **30**.[28] Quenching with diethylamine yielded, in a similar fashion, the *N,N*-diethyloxalylamide **31**. The oxindole **32** was prepared by treating **4** with pyridinium hydrobromide perbromide in aqueous acetic acid. Similar, but not identical, conditions have been described earlier for the preparation of oxindoles.[29-32] Mannich conditions afforded the gramine analog **33**.[28] Reduction of **5** with lithium aluminum hydride yielded the methyl compound **34**. Indole N-methylation of **5** with methyl iodide yielded compound **35**. Treatment of compound **5** with sulfenyl chloride (freshly prepared from sulfuryl chloride and dimethyl disulfide) according to Tupper *et al.*[33] afforded the thiomethyl derivative **36**, which was oxidized to the corresponding methylsulfone **37** with *m*-chloroperbenzoic acid.

Pharmacology

Biochemistry. The *in vivo* biochemical test utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neurone.[34] Dopamine (DA) and noradrenaline (NA) have the same general biosynthetic pathway, and the synthesis rates of these catecholamines are decreased by agonists (and increased by antagonists) at dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT receptor agonists.[2,35,36] The accumulation of 5-HTP, following decarboxylase inhibition by means of (3-hydroxybenzyl)hydrazine (NSD 1015), was used as an indicator of the 5-HT synthesis rate in three different brain areas (Table 2). In addition, DOPA accumulation was used as an indicator of the DA synthesis rate in the DA rich areas (*i.e.*, limbic system and corpus striatum) and the NA synthesis rate in the NA rich hemispheres (mainly cortex). For this study we used reserpine-pretreated rats (5 mg/kg sc, 18 h), in which the synthesis rate of especially DOPA is raised via feedback regulation. This behavioral and biochemical model is designed to detect directly acting agonists at central monoamine receptors.

***In Vitro* Binding.** The abilities of the test compounds to displace the radioactively labeled ligands [^{3}H]-U86170, [^{3}H]spiperone, [^{3}H]-8-OH-DPAT, and [^{3}H]-serotonin from D_2, D_3, 5-HT_{1A}, and 5-HT_{1D} receptor sites, respectively, were determined in CHO-K1 cells with expressed mammalian receptors.

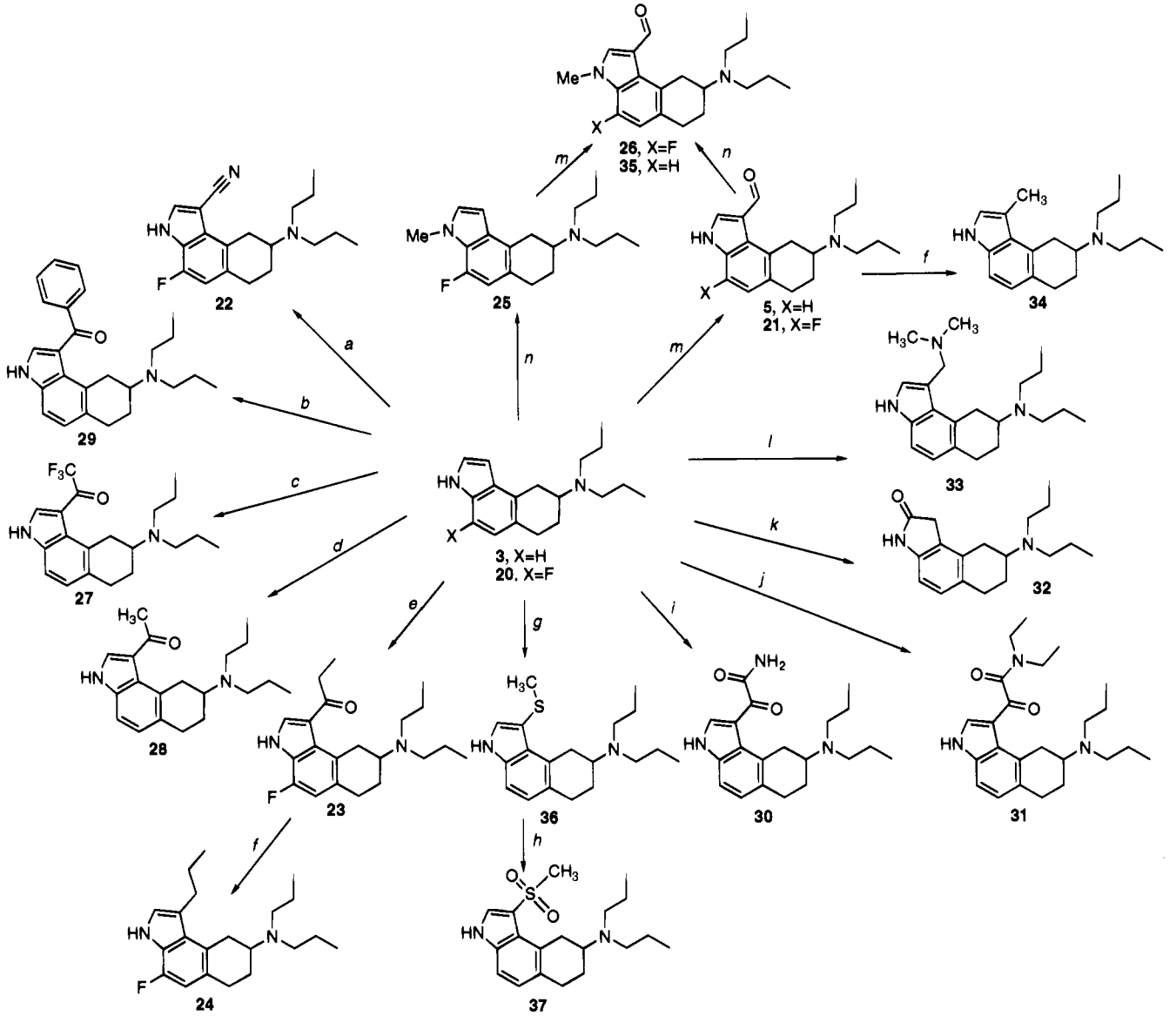
Oral Bioavailability. The oral bioavailability in rats was determined by means of analysis of the actual plasma concentrations after oral and intravenous administration.

Results and Discussion

As mentioned in the introduction, several compounds, which previously had been tested for 5-HT_{1A} affinities in rat brain homogenate,[7,9] were rerun in CHO cells. These new values were well correlated to the previous runs ($R^2 = 0.8$) with approximately 8 times lower values for CHO cells.

The 4-fluorinated analogs **20**−**22** showed a striking resemblance in pharmacological profile to the corresponding nonfluorinated analogs **4**, **5**, and **8**. Thus, the

Scheme 2. Preparation of Derivatives with Various Aromatic Substituents[a]

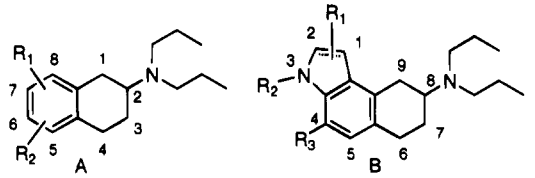


[a] (a) 1. $ClSO_2NCO$, MeCN, rt, 20 min, 2. DMF rt, 1 h; (b) 1. Me_2NCOPh, $POCl_3$, 84 °C, 2 h, 2. NaOH; (c) TFAA, DMF, rt, 31 h; (d) 1. Me_2NCOMe, $POCl_3$, 85 °C, 3 h, 2. NaOH; (e) Me_2NCOEt, $POCl_3$, 80 °C, 3 h, 2. NaOH; (f) $LiAlH_4$, ether, rt, 2 h; (g) $(MeS)_2$, SO_2Cl_2, CH_2Cl_2, 0 °C, 2 h; (h) *m*-CPBA, CH_2Cl_2, rt, 5 h; (i) 1. $(COCl)_2$, ether, 0 °C to rt, 20 min, 2. NH_3; (j) 1. $(COCl)_2$, ether, 0 °C, 20 min, 2. Et_2N; (k) $PyrHBrBr_2$, aq HOAc, 80 °C, 5 h; (l) HOAC, aq HCHO, aq Me_2NH, dioxane, 0 °C, 2 h; (m) 1. DMF, $POCl_3$, 50 °C, 1 h, 2. NaOH; (n) 1. NaH, DMF, 20 min, 2. MeI, 1 h.

1-unsubstituted compounds **20**, *R*-(+)-**20**, and *S*-(−)-**20** had affinities similar for 5-HT_{1A} receptors as compounds **4**, *R*-(+)-**4**, and *S*-(−)-**4**. The selectivity with respect to other receptors was almost identical except for D_3 receptors, for which the fluorinated compound **20** had a relatively high affinity. In addition, the highly potent and quite selective formyl-substituted 4-fluoro compounds **21**, *R*-(+)-**21**, and *S*-(−)-**21** were pharmacologically similar to **5**, *R*-(+)-**5**, and *S*-(−)-**5**. The 1-cyano derivative **22**, however, showed less affinity for 5-HT_{1A} receptors than the corresponding analog **8**. This difference was not detectable *in vivo*. Consequently, an introduction of a fluorine substituent in the 4-position of the pyrroloaminotetralin ring system did not change the pharmacological response of this series of compounds.

From the recent results of Liu *et al.*[37] in the aminotetralin series (where the 8-acetyl derivatives showed to be highly potent 5-HT_{1A} agonists), one might by analogy suspect that a 1-substituted acetyl group in the pyrroloaminotetralin series also would be highly potent. This would also be suspected by extrapolation from the fact that the 1-formyl derivatives **5** and **21** are very potent. Interestingly, this was not the case. The acetyl derivative **28** showed a 70-fold lower affinity for 5-HT_{1A} receptors as compared to compound **5**. This is also reflected by the *in vivo* studies. Other acyl homologs, **23**, **27**, and **29**, showed a similar trend. The oxalylamide derivative **30** showed an affinity similar to that of the 1-trifluoroacetyl derivative **27**, but only a partial response could be detected in the 5-HTP accumulation assay. The *N,N*-diethyl derivative **31** showed a higher affinity than hydrogen homolog **30**. For all these acyl analogs, the affinity was also low for dopamine receptors. Going from an acyl derivative to an alkyl derivative as in the 4-fluoro, 1-propyl analog **24** did not severely change the 5-HT_{1A} binding. The D_2 receptor binding affinity was, however, significantly increased. The 5-HT_{1A} affinities of the 1-methyl (**34**) and 1-thiomethyl (**36**) derivatives were similar to those of most of

Table 1. *In Vitro* Binding Profile of Discussed and Synthesized Compounds



compd	type	substitution			*in vitro* binding[a] K_i (nM)				
		R_1	R_2	R_3	5-HT_{1A}	5-$HT_{1D\alpha}$	5-$HT_{1D\beta}$	D_2	D_3
1	A	8-OH	H		0.5 ± 0.02	164 ± 30	638 ± 75	1126 ± 114	333 + 29
4	B	H	H	H	3.3 ± 0.5	40 ± 14	349 ± 125	15 ± 0.8	37 ± 5
(+)-**4**	B	H	H	H	5.2 ± 0.8	16 ± 7	139 ± 62	7.4 ± 1	30 ± 30 ± 4
(−)-**4**	B	H	H	H	1.4 ± 0.2	440 ± 65	2275 ± 246	17 ± 2	22 ± 2
5	B	1-CHO	H	H	0.2 ± 0.03	173 ± 54	364 ± 84	40 ± 6	70 ± 17
(+)-**5**	B	1-CHO	H	H	0.2 ± 0.03	31 ± 7	210 ± 55	17 ± 3	51 ± 6
(−)-**5**	B	1-CHO	H	H	0.2 ± 0.03	155 ± 48	939 ± 241	423 + 92	751 ± 116
8	B	1-CN	H	H	0.4 ± 0.1	7.5 ± 0.7	38 ± 2	24 ± 1	43 ± 3
(+)-**8**	B	1-CN	H	H	0.8 ± 0.2	6.7 ± 0.5	26 ± 3	22	45 ± 3
(−)-**8**	B	1-CN	H	H	0.5 ± 0.1	42 ± 3	304 ± 16	419 ± 65	391 ± 59
9	B	1-Cl	H	H	2.0 ± 0.4	23 ± 1	I[b]	9.8 ± 0.8	15 ± 3
10	B	1-CF_3CH_2	H	H	18 ± 1	54 ± 8	409 ± 41	86 ± 4	134 ± 6
15	A		see Scheme 1		134 ± 10	585 ± 59	1512 ± 179	162 ± 14	156 ± 23
19	A	5-NH_2	6-F		123 ± 20	762 ± 39	2024 ± 274	86 ± 5	77 ± 11
20	B	H	H	F	1.4 ± 0.2	11 ± 3	216 ± 14	2.8 ± 1	1.6 ± 0.4
(+)-**20**	B	H	H	F	1.5 ± 0.3	14 ± 1	142 ± 19	7.8 ± 0.5	14 ± 4
(−)-**20**	B	H	H	F	3.7 ± 0.4	294 ± 17	948 ± 129	4.4 ± 0.4	4.1 ± 1.3
21	B	1-CHO	H	F	0.5 ± 0.1	4.6 ± 0.4	82 ± 3	65 ± 14	65 ± 7
(+)-**21**	B	1-CHO	H	F	0.3 ± 0.1	4.4 ± 0.4	NT[c]	48 ± 3	55 ± 8
(−)-**21**	B	1-CHO	H	F	0.8 ± 0.1	34 ± 3	179 ± 32	199 ± 26	78 ± 17
22	B	1-CN	H	F	2.3 ± 0.5	8.6 ± 1.4	121 ± 9	72 ± 5	63 ± 5
23	B	1-COC_2H_5	H	F	7.1 ± 0.5	36 ± 3	I	377 ± 66	542 ± 42
24	B	*n*-Pr	H	F	11 ± 2	8.4 ± 1	177 ± 15	5.9 ± 1.2	111 ± 10
25	B	H	Me	F	250 ± 29	217 ± 23	1654 ± 194	86 ± 5	52 ± 5
26	B	1-CHO	Me	F	28 ± 1	419 ± 35	618 ± 68	1034 ± 236	572 ± 110
27	B	1-$COCF_3$	H	H	20 ± 4	112 ± 6	279 ± 115	544 ± 65	675 ± 147
28	B	1-$COCH_3$	H	H	14 ± 1	108 ± 6	587 ± 63	206 ± 29	320 ± 41
29	B	1-COC_6H_6	H	H	8.6 ± 1	NT	NT	177 ± 20	108 ± 15
30	B	1-$COCONH_2$	H	H	24 ± 3	87 ± 12	552 ± 188	I	NT
R-(+)-**30**	B	1-$COCONH_2$	H	H	17 ± 3	54 ± 6	856 ± 121	472 ± 48	I
S-(−)-**30**	B	1-$COCONH_2$	H	H	49 ± 9	440 ± 39	1096 ± 147	I	I
31	B	1-$COCONEt_2$	H	H	7.3 ± 1.2[d]	NT	NT	NT	NT
32	B	2-=O, 1-H_2	H	H	14 ± 3	26 ± 2	194 ± 9	11 ± 2	23 ± 2
33	B	1-CH_2NMe_2	H	H	113 ± 6	I	I	I	I
34	B	1-Me	H	H	13 ± 3	43 ± 4	789 ± 129	14 ± 2	67 ± 12
35	B	1-CHO	Me	H	40 ± 3	334 ± 193	439 ± 305	510 ± 113	1012 ± 163
36	B	1-SMe	H	H	13 ± 2	18 ± 1	I	33 ± 1	55 ± 7
37	B	1-SO_2Me	H	H	11 ± 2	52 ± 3	373 ± 79	265 ± 59	I

[a] For 5-HT_{1A}: CHO cells [^{3}H]-8-OH-DPAT. For D_2: CHO cells [^{3}H]U86170. [b] I = inactive (less than 50% inhibition at 1 μM). [c] NT = not tested. [d] Calf caudate hippocampus.

the acyl derivatives (**27**−**31**) and the propyl derivative **24** and nonselective vs D_2 receptors. The 1-thiomethyl derivative **36** seemed to be a moderately active agonist *in vivo* in both dopaminergic and serotonergic systems. Oxidation of this moiety to the 1-methylsulfone **37** retained the 5-HT_{1A} receptor affinity but lowered the affinity for D_2 receptors. A different type of substituent is represented by the gramine derivative **33**, which contains a basic amine moiety. The low overall affinity and *in vivo* activity of this compound may be explained partly by protonation of the amine under physiological conditions, and this could severely affect the 5-HT_{1A} affinity (gramine pK_a = 8.52[38,39]). In the case of the oxindole **32,** although the aromaticity of the pyrrolo ring is lost, there still is a possibility for hydrogen-bonding acceptance from the oxo part of the amide moiety. The 5-HT_{1A} affinity (K_i = 14 nM) is similar to most of the moderate affinity compounds in this series (acyl, propyl, thiomethyl, etc.). Interestingly, the potency in 5-HTP accumulation is relatively higher than that of the other compounds tested with an equivalent 5-HT_{1A} affinity. The D_2 receptor affinity is relatively high for **32** compared to other compounds in this series.

A question mentioned in the introduction was the importance of the indole NH hydrogen for 5-HT_{1A} activity. To investigate its influence on the 5-HT_{1A} affinity and *in vivo* potency, the 3-methyl derivatives **25**, **26**, and **35** were prepared. All of these compounds had significantly lower 5-HT_{1A} affinities as compared to their corresponding nonmethylated analogs **20**, **21**, and **5**. This implies that, for this type of 5-HT_{1A} agonists, the indole NH moiety is crucial for drug−receptor interaction. Steric effects may also be involved.

The affinities for dopamine D_3 receptors for most of the compounds of this study seem to correlate with their affinities for the D_2 receptors with weak variations. A striking exception is the 4-fluoro 1-propyl compound **24**, which discriminates between D_2 and D_3 receptors with a 20-fold preference for D_2 receptors.

Table 2. Biochemistry: *In Vivo* Results by Means of DOPA and 5-HTP Accumulation[a]

compd	type	R_1	R_2	R_3	DOPA accum ED_{50} (μmol/kg) limb	DOPA accum ED_{50} (μmol/kg) stri	DOPA accum ED_{50} (μmol/kg) hem	5-HTP-accum ED_{50} (μmol/kg) limb	5-HTP-accum ED_{50} (μmol/kg) stri	5-HTP-accum ED_{50} (μmol/kg) hem
1[b]	A	8-OH	H		I[c](45)	I(45)	I(45)	0.052	0.052	0.063
4[e]	B	H	H	H	0.15 (6.82 ± 0.26)	0.30 (6.52 ± 0.30)	I(12.5)	0.096 (7.02 ± 0.58)	0.076 (7.1 ± 1.2)	0.17 (6.77 ± 0.40*)
(+)-**4**[e]	B	H	H	H	0.15# (6.81 ± 0.43)	0.18 (6.75 ± 0.22)	I(3.1)	0.21 (6.69 ± 0.31)	0.17 (6.77 ± 0.41*)	0.28 (6.55 ± 0.42)
(−)-**4**[e]	B	H	H	H	0.51# (6.29 ± 0.60)	0.82 (6.09 ± 0.75)	I(3.1)	0.21 (6.69 ± 0.38)	0.34 (6.46 ± 0.78)	0.23 (6.63 ± 0.46)
5[e]	B	1-CHO	H	H	0.30 (6.52 ± 0.64*)	3.34 (5.48 ± 0.08*)	I(12.5)	0.11 (6.96 ± 0.29)	0.067 (7.18 ± 0.39)	0.13 (6.88 ± 0.30)
(+)-**5**[e]	B	1-CHO	H	H	I(3.1)	I(3.1)	I(3.1)	0.072 (7.14 ± 0.33)	0.12 (6.91 ± 0.44*)	0.45 (6.34 ± 0.20*)
(−)-**5**[e]	B	1-CHO	H	H	P[d](12.5)	P(12.5)	I(12.5)	0.11 (6.94 ± 0.81)	0.0052 (8.28 ± 1.04)	0.032 (7.49 ± 0.49)
(+)-**6**[e]	B	2-CN	H	H	2.01 (5.69 ± 0.29*)	3.36 (5.47 ± 0.07*)	I(12.5)	0.21 (6.67 ± 0.17)	0.079 (7.10 ± 0.46)	0.28 (6.56 ± 0.34
8[e]	B	1-CN	H	H	1.05 (5.98 ± 0.20*)	3.2 (5.49 ± 0.12*)	P(12.5)	0.17 (6.77 ± 0.21)	0.22 (6.65 ± 0.33)	0.45 (6.35 ± 0.46)
(+)-**8**[e]	B	1-CN	H	H	P(3.1)	I(3.1)	I(3.1)	0.092 (7.03 ± 0.22)	0.036 (7.44 ± 0.91)	0.14 (6.85 ± 0.30)
(−)-**8**[e]	B	1-CN	H	H	P(50)	P(50)	I(50)	0.12 (7.93 ± 0.22)	0.089 (7.05 ± 0.28)	0.15 (6.81 ± 0.32)
9[e]	B	1-Cl	H	H	3.7 (5.43 ± 0.22)	3.4 (5.47 ± 0.16)	P(50)	1.4 (5.86 ± 0.65)	1.7 (5.78 ± 0.49)	1.4 (5.85 ± 0.60)
10[e]	B	1-CF_3CH_2	H	H	I(50)	P(50)	I(50)	I(50)	I(50)	I(50)
11[e]	B		see Figure 1		P(50)	P(50)	I(50)	P(50)	I(50)	I(50)
12[e]	B		see Figure 1		P(50)	P(50)	I(50)	I(50)	I(50)	I(50)
15	A		see Scheme 1		I(50)	I(50)	I(50)	15.5 (4.81 ± 0.69)	9.53 (5.02 ± 0.55)	12.8 (4.89 ± 0.48)
19	A	5-NH_2	6-F		4.62 (5.33 ± 0.27*)	3.80 (5.42 ± 0.20)	14.5 (4.84 ± 0.37*)	5.06 (5.30 ± 0.63*)	1.61 (5.8 ± 1.0*)	8.39 (5.07 ± 0.50*)
20	B	H	H	F	1.17# (5.9 ± 0.23)	1.00# (6.00 ± 0.21)	I(12.5)	1.92 (5.72 ± 0.18*)	0.06 (7.23 ± 0.46*)	0.54 (6.27 ± 0.33)
(+)-**20**	B	H	H	F	0.49 (6.31 ± 0.12*)	0.63 (6.20 ± 0.15*)	I(12.5)	0.53 (6.27 ± 0.20*)	0.70 (6.16 ± 0.23*)	0.51 (6.29 ± 0.25*)
(−)-**20**	B	H	H	F	0.80# (6.10 ± 0.10)	0.43# (6.36 ± 0.32)	I(12.5)	0.74 (6.13 ± 0.46)	0.42 (6.37 ± 0.20*)	0.83 (6.08 ± 0.17)
21	B	1-CHO	H	F	P(50)	P(50)	I(12.5)	0.079 (7.10 ± 0.36)	0.042 (7.38 ± 0.36)	0.027 (7.56 ± 0.50*)
(+)-**21**	B	1-CHO	H	F	P(12.5)	P(12.5)	I(12.5)	0.078 (7.11 ± 0.14)	0.083 (7.08 ± 0.32)	0.084 (7.07 ± 0.26)
(−)-**21**	B	1-CHO	H	F	P(12.5)	P(12.5)	I(12.5)	0.23 (6.65 ± 0.23)	0.17 (6.78 ± 0.33)	0.32 (6.49 ± 0.72)
22	B	1-CN	H	F	0.55 (6.26 ± 0.20)	2.10 (5.68 ± 0.86)	I(12.5)	0.52 (6.28 ± 0.42)	0.43 (6.37 ± 0.36)	0.46 (6.33 ± 0.50)
23	B	1-COC_2H_5	H	F	P(40)	P(40)	I(40)	6.34# (5.20 ± 0.90)	3.94# (5.40 ± 0.42*)	P(40)
26	B	1-CHO	Me	F	P(20)	P(20)	I(20)	P(20)	P(20)	P(20)
27	B	1-$COCF_3$	H	H	20.8 (4.68 ± 0.22*)	12.6 (4.90 ± 0.12*)	I(50)	12.6 (4.90 ± 0.22)	6.5 (5.2 ± 1.0)	16.3 (4.79 ± 0.24)
28	B	1-$COCH_3$	H	H	P(50)	P(50)	I(50)	15.5	16.0	13.0
30	B	1-$COCONH_2$	H	H	P(50)	P(50)	P(50)	P(50)	P(50)	P(50)
32	B	2-=O, 1-H_2	H	H	0.17 (6.77 ± 0.15)	0.25 (0.25 ± 0.11)	I(50)	0.45 (6.35 ± 0.39)	0.41 (6.39 ± 0.22)*	0.86 (6.07 ± 0.46)
33	B	1-CH_2NMe_2	H	H	I(12.5)	I(12.5)	I(12.5)	I(12.5)	I(12.5)	I(12.5)
35	B	1-CHO	Me	H	P(20)	P(20)	I(20)	P(20)	P(20)	P(20)
36	B	1-SMe	H	H	7.11 (5.15 ± 0.32)	5.23 (5.23 ± 0.16)	I(25)	10.0 (5.00 ± 0.54*)	10.2 (5.00 ± 0.50*)	P(12.5)

[a] ED_{50} values calculated as in ref 7. An asterisk indicates that fixed values were introduced for slope. A pound sign designates ED_{50} for a partial reduction. Confidence limits (95%) are given in parentheses for pED_{50}. [b] Data from ref 1. [c] I = inactive at the highest dose tested. [d] P = significant partial reduction only at the highest dose tested. [e] Data from ref 7.

Even though none of the compounds of this study seems to be selective for either of the 5-HT_{1D} receptors over the 5-HT_{1A} receptor, it is of interest that many of the compounds do discriminate between 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. To our knowledge, no such compounds have yet been reported in the literature. All the compounds described here show a preference for 5-$HT_{1D\alpha}$. The most striking examples are compounds **22** and **24**, which have a 14- and 21-fold preference for 5-$HT_{1D\alpha}$, respectively. A detectable trend is that the fluoro-substituted compounds seem to be slightly more selective with respect to 5-HT_{1D} receptors than their corresponding nonfluorinated compounds. On the other hand, the fluorinated compounds are not as selective for the 5-HT_{1A} receptor vs the 5-HT_{1D} receptors as their corresponding nonfluorinated analogs. Another trend is that the (−)-*S*-enantiomers are more selective for the 5-HT_{1A} receptors.

The 4-fluoro 1-cyano compound **22** was tested for oral bioavailability in rats to compare with the highly bioaccesible nonfluorinated analogs *R*-(+)-**5**, *S*-(−)-**5**, *R*-(+)-**6**, and **8**. Surprisingly, compound **22** did not show the high oral bioavailability of the nonfluorinated compounds. It is not clearly understood why this

Table 3. Pharmacokinetics

compd	dose (pmol/g/h)	AUC (pmol/mL)	C_{max} (min)	t_{max} (h)	$t_{1/2}$ iv (%)	F (iv/po)[b] (%)	ED_{50} ratio[a] (sc/po)
1[c]	iv 1.0	213 ± 53	344 ± 93	3 ± 1	1.2	2.4 ± 0.9[d]	2
	po 20.0	104 ± 36	63 ± 32	29 ± 9			
R-(+)-**3**[c]	iv 2.0	431 ± 14	712 ± 38	2 ± 0	1.5	46 ± 16[e]	15
	po 10.0	848 ± 276	108 ± 63	150 ± 82			
S-(−)-**3**[c]	iv 2.0	607 ± 65	849 ± 35	2 ± 0	1.0	72 ± 12[f]	18
	po 10.0	2224 ± 371	606 ± 80	48 ± 17			
R-(+)-**6**[c]	iv 4.0	1817 ± 252	2566 ± 528	4 ± 2	1.5	63 ± 7	38
	po 10.0	2857 ± 300	1116 ± 171	75 ± 42			
8[c]	iv 5.0	1115 ± 94	1733 ± 138	2 ± 0	1.5	54 ± 13[e]	NT
	po 40.0	4849 + 1182	1504 ± 406	135 ± 15			
22	iv 54.0	238 ± 13	547 ± 212	2 ± 0	2.5	8.1 ± 1.6[e]	NT
	po 10.0	48 + 10	18 ± 2	33 ± 15			

[a] Determined as the ratio of the 5-HTP accumulation decrease in limbic regions after oral and subcutaneous administration (see Table 1). [b] Blood plasma levels in rats. Calculated from total area from [C] vs time curves unless otherwise stated. [c] Data from refs 7 and 9. [d] SEM, $n = 5$. [e] SEM, $n = 4$. [f] SEM, $n = 6$. All other values are given with SEM, $n = 4-6$.

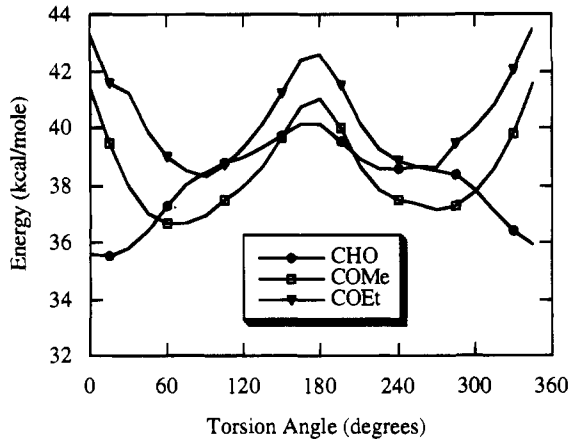


Figure 4. Drivers perfomed on the torsion angle defined by C2−C1−C'1−O. The CHO substituent of the more potent compound **5** shows minimum energy at 0° (s-cis conformation), whereas the minimum energy for the other less potent acyl analogs (here exemplified with COMe and COEt) lies 60−90° off-plane.[41]

seemingly small difference has such a negative impact on the bioavailability.

The wide range of receptor affinities and *in vivo* potencies from this set of analogs with seemingly small differences, which is partly due to a rational choice of substituents (*i.e.*, PCA maps), makes this material suitable for a deeper QSAR investigation. The results using principal least squares regression will be presented in a subsequent article.[40] However, some interesting SAR findings can be extracted without advanced statistical methods. The fact that the formyl derivatives **5** and **21** were more potent than the other acyl analogs (**23**, **28**−**31**) may be explained by torsional barriers. The s-cis conformation ($\tau = 0°$; Figure 4) of the acyl moiety is favored only for the formyl compounds, whereas torsional drivers of other less potent acyl analogs reveal that the minima are off-plane (Figure 4).[41] This may support our previous suggestions for the alignment of these ligands with interacting points of the receptor protein (Figure 5).[7] Another interesting finding is the dramatic decrease in potency for the indole *N*-methyl compounds **25**, **26**, and **35** compared with the corresponding non-N-methylated compounds **20**, **21**, and **5**, which suggests that the indole NH moiety is crucial in the interaction with the 5-HT_{1A} receptor protein for this series of compounds. The sketch of Figure 5 shows how this can be accomplished with an interaction point to an additional serine or threonine residue of the receptor protein. Also, among this series of compounds examples of discrimination between serotonin 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors have been found. Even though their major affinity preference is for the 5-HT_{1A} receptors, this information is potentially useful for medicinal chemists in the field of serotonin research.

Experimental Section

Chemistry. Magnetic resonance spectra were recorded on a Varian VXR4000 300 MHz spectrometer using tetramethylsilane as the internal standard. ^{13}C NMR spectra (see supplementary material) were assigned in most of the cases with the use of the attached proton test (APT). The numerous ^{13}C and ^{1}H resonances of amides **16**−**18** are due to rotamers. F-containing compounds gave ^{13}C NMR spectra with coupled signals. Mass spectra were recorded on a HP5970A mass selective detector working at 70 eV and interfaced with a HP 5700A gas chromatograph. Elemental analysis values (C, H, N) for new and biologically tested substances where within 0.4% of the theoretical values (Mikrokemi AB), unless indicated with an asterisk. Melting points were determined using a Reichert Thermovar microscope and are uncorrected. All physical data (except for mp and elemental anal.) on amines were obtained on the free bases. Chromatography on silica gel was performed using flash chromatography. Compounds **4** and **5** were prepared as described in refs 9, 20, or 27. Yields have not been optimized.

6-Fluoro-3,4-dihydro-1*H*-naphthalen-2-one (14). A solution of 4-fluorophenylacetic acid (100 g, 0.65 mol) and thionyl chloride (164 g, 1.37 mol) in dichloromethane (200 mL) was refluxed for 4 h. The mixture was cooled and then evaporated to yield the acid chloride which was redissolved in dichloromethane (200 mL) and added to a cooled (−5 °C) suspension of aluminum trichloride (240 g, 1.80 mol) in dichloromethane (1000 mL). After the mixture was stirred for 5 min, a gentle stream of ethene was led through the reaction mixture for 5 h. The resulting mixture was cautiously poured into ice and concentrated hydrochloric acid. After shaking, the layers were separated and the organic layer was washed with 10% sodium carbonate. The solution was dried (magnesium sulfate), filtered, and evaporated to yield 140 g of a crude product, which was subjected to a silica gel column and eluted using 2,2,4-trimethylpentane/diethyl ether (1:1) as eluant: yield 80.0 g (75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (t, 2H), 3.05 (t, 2H), 3.55 (s, 2H), 6.90 (m, 2H), 7.1 (m, 1H); MS *m/e* 164 (M^+, 53), 122 (100), 135 (35), 133 (14), 96 (10).

(6-Fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)propylamine (15). To a solution of 6-fluoro-3,4-dihydro-1*H*-naphthalen-2-one (**14**) (77.5 g, 0.47 mol) in methanol (750 mL) were added separately acetic acid (30 mL), 1-propylamine (30 mL, 41.7 g, 0.70 mol), and sodium cyanoborohydride (60 g, 0.93 mol). The resulting mixture was stirred for 5 h at ambient temperature, and 10% hydrochloric acid (200 mL) was thereafter added dropwise (*CAUTION! HCN evolves*) followed by water (125 mL). After stirring overnight, the volume of the mixture was reduced by evaporation. Diethyl ether, water,

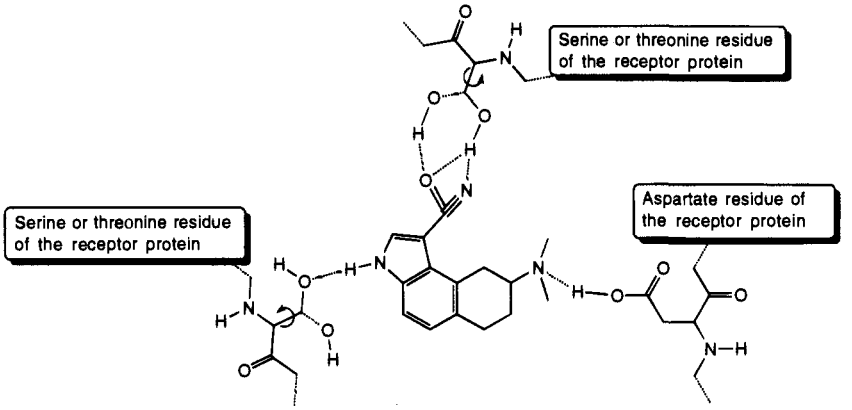


Figure 5. Compounds **5** and **6** overlapped in an extended version of the sketch of ref 7. The sketch shows possible modes of interaction between this type of compound and amino acid residues of the 5-HT_{1A} receptor protein. The low affinity of the indole N-methylated compounds may reflect that an interaction between the NH of the indole part and the receptor protein (here represented by a serine or threonine residue, see left) is needed for high affinity in this series of compounds.

and 10% sodium carbonate were added until basic reaction occurred. The mixture was shaken, separated, and extracted two additional times with diethyl ether. The combined organic extracts were dried (magnesium sulfate), filtered, and evaporated to yield 87 g of the product (91%), sufficiently pure for further synthesis. For analytical purposes the HCl salt was prepared from HCl/methanol and recrystallized from methanol/diethyl ether: mp 283–285 °C (HCl salt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.50 (sxt, 2H), 1.55 (m, 1H), 2.05 (br d, 1H), 2.50 (m, 1H), 2.65 (t, 2H), 2.7–3.1 (m, 5H), 6.75 (m, 2H), 7.0 (t, 1H); MS *m/e* 207 (M^+, 42), 149 (100), 178 (70), 147 (17), 109 (15). Anal. ($C_{13}H_{18}FN$·HCl) C, H, N.

***N*-(6-Fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (16).** Propionyl chloride (39.4 mL, 37.0 g, 0.40 mol) was added dropwise to a solution of (6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)propylamine (**15**) (83.0 g, 0.40 mol) in dichloromethane (370 mL) and triethylamine (50 mL). The solution was stirred at ambient temperature for 1.5 h and then washed with 10% sodium carbonate, dried (magnesium sulfate), filtered, and evaporated to yield 118 g (112%) of crude product. This material was used without further purification in the next step. Analytical samples were prepared by separation on a silica gel column (hexane/diethyl ether, 2:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (q, 3H), 1.15 (q, 3H), 1.60 (sxt, 2H), 1.95 (sxt, 2H), 2.40 (sxt, 2H), 2.7–3.0 (m, 4H), 3.15 (m, 2H), 4.0 (sept, 0.4H), 4.60 (sept, 0.6H), 6.8 (m, 2H), 7.0 (m, 1H); MS *m/e* 263 (M^+, 0.2), 148 (100), 116 (74), 149 (30), 133 (10). Anal. ($C_{16}H_{22}FNO$) C, H,* N; H calcd 8.42, found 7.9.

***N*-(6-Fluoro-7-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (17c), *N*-(6-Fluoro-8-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (17a), and *N*-(6-Fluoro-5-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (17b).** To a solution of *N*-(6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (**16**) (30 g, 0.11 mol) in nitromethane (200 mL) was added dropwise at −5 °C nitric acid as a 33% solution in concentrated sulfuric acid (40 mL). The mixture was stirred for 30 min and then poured on ice and extracted three times with diethyl ether. The combined ethereal extracts were washed (10% sodium carbonate), dried (magnesium sulfate), filtered, and evaporated to yield 14 g of an isomeric mixture. Purification on a silica gel column using diethyl ether as eluant yielded 2.7 g of a mixture of three isomers and 4.4 g of pure *N*-(6-fluoro-7-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (**17c**). For analytical purposes the mixed fraction was subjected to another chromatography (hexane/ethyl acetate, 4:1–1:1), giving some pure fractions of the three possible isomers eluting in the named order.

17a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.20 (t, 3H), 1.65 (oct, 2H), 2.0 (m, 2H), 2.40 (q, 2H), 2.8–3.3 (m, 6H), 4.0 (m, 0.25H), 4.45 (sept, 0.75H), 7.08 (dd (0.75) and dd (0.25), J = 8.4, 2.2 Hz, 1H), 7.47 (dd, J = 8.1, 2.2 Hz, 0.75H), 7.53 (dd, J = 8.1, 2.2 Hz, 0.25H); MS *m/e* 308 (M+, 0.2), 291 (100), 223 (44), 57 (44), 116 (34). Anal. ($C_{16}H_{21}FN_2O_3$·$^1/_2H_2O$) C, H, N.

17b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.20 (t, 3H), 1.60 (sxt, 2H), 2.0 (sxt, 2H), 2.35 (q, 2H), 2.8–3.3 (m, 6H), 4.03 (m, 0.25H), 4.45 (sept, 0.75H), 7.03 (quintet, 1H), 7.17 (m, 1H); MS *m/e* 308 (M^+, 0.2), 116 (100), 176 (37), 57 (35), 223 (18). Anal. ($C_{16}H_{21}FN_2O_3$) C, H, N.

17c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.20 (t, 3H), 1.65 (sxt, 2H), 2.05 (m, 2H), 2.40 (q, 2H), 2.8–3.3 (m, 6H), 4.05 (m, 0.25H), 4.50 (sept, 0.75H), 7.08 (d (0.75) and d (0.25), J = 11.6 Hz, 1H), 7.76 (d, J = 7.4 Hz, 0.75H), 7.82 (d, J = 7.4 Hz, 0.25H); MS *m/e* 308 (M+, 1), 116 (100), 57 (45), 193 (29), 163 (21), 86 (16). Anal. ($C_{16}H_{21}FN_2O_3$·$^1/_2H_2O$) C, H, N.

***N*-(7-Amino-6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (18).** A mixture of *N*-(6-fluoro-7-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (**17c**) (4.40 g, 14.3 mmol) and 10% Pd/C (0.3 g) in absolute ethanol (200 mL) was hydrogenated in a Parr apparatus for 18 h. The mixture was filtered (Celite) and evaporated to yield 3.7 g (93%) of pure product: mp 88–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (q, 3H), 1.15 (q, 3H), 1.60 (m, 2H), 1.90 (m, 2H), 2.35 (m, 2H), 2.5–3.0 (m, 4H), 3.05–3.30 (m, 2H), 3.6 (br s, 2H), 4.0 (m, 0.5H), 4.6 (m, 0.5H), 6.45 and 6.49 (two d, J = 9.1 or 11.4 Hz, 1H), 6.70 (t or two d, J = 10.5 Hz, 1H); MS *m/e* 278 (M^+, 0.3), 163 (100), 162 (29), 164 (15), 148 (8), 137 (8). Anal. ($C_{16}H_{23}FN_2O$) C, H, N.

6-Fluoro-N^2,N^2-dipropyl-1,2,3,4-tetrahydronaphthalene-2,7-diamine (19). To a solution of *N*-(7-amino-6-fluoro-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-propylpropionamide (**18**) (3.7 g, 13.3 mmol) in dry diethyl ether (200 mL) was added portionwise lithium aluminum hydride (1.1 g, 29 mmol). After stirring for 2 h, water (1.1 mL), 15% sodium hydroxide (1.1 mL), and water (3.3 mL) were cautiously added in consecutive order. The mixture was stirred for 20 min, filtered, and evaporated to yield 3.3 g (94%) of a pure product. The di-HCl salt was prepared in HCl/ethanol and recrystallized from methanol/diethyl ether for analytical purposes: mp 144–146 °C (di-HCl salt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.45 (q, 4H), 1.95 (m, 1H), 2.45 (m, 4H), 2.5–2.9 (m, 6H), 3.40 (s, 2H), 6.48 (d, J = 9.0 Hz, 1H), 6.68 (d, J = 11.7 Hz, 1H); MS *m/e* 264 (M^+, 17), 164 (100), 235 (55), 163 (22), 138 (20), 147 (16). Anal. ($C_{16}H_{25}FN_2$·2HCl·H_2O) C, H, N.

(4-Fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (20). A mixture of 6-fluoro-N^2,N^2-dipropyl-1,2,3,4-tetrahydronaphthalene-2,7-diamine (**19**) (3.0 g, 11.3 mmol), chloral hydrate (2.04 g, 12.3 mmol), hydroxylammonium hydrochloride (2.48 g, 35.7 mmol), and sodium sulfate (12.6 g) in distilled water (46 mL) was refluxed for 1.5 h and then cooled to ambient temperature. Ammonia (5% in water) was added. The resulting mixture was extracted three times with ethyl acetate, and the combined organic extracts were dried (magnesium sulfate), filtered, and evaporated to a residue of 3.80 g. This material was cooled to −15 °C and then subjected to a cooled (−15 °C) solution of concentrated sulfuric acid (68 mL) and distilled water (6.8 mL). The resulting mixture was heated to 80 °C and maintained at that temperature for 45 min. After cooling, the mixture was poured onto ice (500 mL)

and subsequently made basic by the dropwise addition of ammonia (32%). A similar workup procedure as above yielded 3.5 g (97%) of the dark red isatin: MS *m/e* 318 (M^+, 11), 289 (100), 190 (43), 72 (24), 290 (18), 133 (10).

A solution of this material (1.68 g, 5.3 mmol) in dry diethyl ether (25 mL) was added dropwise to a suspension of lithium aluminum hydride (2.0 g, 53 mmol) in dry diethyl ether (100 mL) at room temperature. The reaction mixture was stirred for 2.5 h, whereafter water (2 mL), 15% sodium hydroxide (2 mL), and water (6 mL) were added successively. After stirring for 20 min, the inorganic salts where filtered off and the resulting solution was evaporated to yield 1.5 g of crude product. Subjecting this material to a silica column and eluting it with petroleum ether/diethyl ether (1:3) yielded 0.70 g (45% total yield) of pure material: mp 112–115 °C (free base); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (q, 4H), 1.70 (m, 1H), 2.05 (m, 1H), 2.52 (t, 4H), 2.7–3.0 (m, 3H), 3.10 (m, 2H), 6.52 (sxt, 1H), 6.64 (d, J =11.8 Hz, 1H), 7.18 (t, J =2.7 Hz, 1H), 8.40 (br s, 1H); MS *m/e* 288 (M^+, 14), 188 (100), 259 (33), 161 (33), 172 (14), 162 (14). Anal. ($C_{18}H_{25}FN_2$) C, H, N.

Resolution of (4-Fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (20, *S*-(−)-20, and *R*-(+)-20). (+)-Di-*p*-toluoyl-D-tartaric acid (2.74 g, 7.11 mmol) and (4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (**20**) (2.05 g, 7.11 mmol) were dissolved separately in ethanol, mixed, and evaporated. The resulting solid was dissolved in a minimum volume of refluxing ethanol (75 mL) and left to crystallize overnight. The recystallization was repeated (five times) until no change in optical rotation was observed (at $[\alpha]^{20}_D$ = +39.8° (c 1.0, methanol). The material obtained was treated with 3 M sodium hydroxide and extracted three times with ethyl acetate to yield 0.50 g (24%) of the *S*-(−)-enantiomer. The free base of the enriched *R*-enantiomer was obtained from the combined mother liquors (workup as above). This material was treated in the same way as described above, now with (−)-di-*p*-toluoyl-L-tartaric acid. After four recrystallizations no change in optical rotation was observed (at $[\alpha]^{20}_D$ = −37.8° (c 1.0, methanol)). After a similar workup, 0.24 g (12%) of the *R*-(+)-enantiomer was recovered.

***S*-(−)-20:** mp 169–170 °C (DTTA salt); $[\alpha]^{20}_D$ −95.2° (c = 1.0, methanol, free base). Anal. ($C_{18}H_{25}FN_2 \cdot C_{20}H_{18}O_{10} \cdot {}^1/_2H_2O$) C, H, N.

***R*-(+)-20:** mp 165–166 °C (DTTA salt); $[\alpha]^{20}_D$ +97.4° (c = 1.0, methanol, free base). Anal. ($C_{18}H_{25}FN_2 \cdot C_{20}H_{18}O_{10} \cdot {}^1/_2H_2O$) C, H, N.

Determination of Optical Purity. The enantiomeric purities of *S*-(−)-**20** and *R*-(+)-**20** were assessed by the use of (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Moshers acid). Upon addition of 1 mol equiv of the acid to a 10 mg/mL solution of **20** in $CDCl_3$, two well-separated signals at δ 7.10 and 7.13 (2-CH resonances) appeared in the ^{1}H NMR spectrum. No traces of the corresponding enantiomer could be detected for either of the enantiomers. The detection limit for the minor enantiomer was estimated to be lower than 1%. The optical purity for both enantiomers was therefore estimated to be >98% ee.

8-(Dipropylamino)-4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (21). To a cooled (−5 °C) solution of phosphorus oxychloride (50 μL, 30.4 mg, 0.20 mmol) in dimethylformamide (3.0 mL) was added a solution of 57 mg (0.20 mmol) of 4-fluoro-8-(*N*,*N*-dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole (**20**) in 2.5 mL of dimethylformamide. After 15 min the resulting mixture was slowly heated to 50 °C and maintained at that temperature for 1 h and then stirred at ambient temperature overnight. The mixture was poured onto ice and basified using 10% sodium hydroxide. After extraction three times with ethyl acetate, the organic layers were dried (magnesium sulfate), filtered, and evaporated to a residue of 45 mg (71%). Purification on a silica gel column using methanol as eluant afforded 20 mg of pure product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (q, 4H), 1.70 (m, 1H), 2.55 (t, 4H), 2.1 (m, 1H), 2.85–3.15 (m, 5H), 3.45 (m, 1H), 6.74 (d, J = 11.1 Hz, 1H), 7.95 (s, 1H), 10.20 (s, 1H); MS *m/e* 316 (M^+, 9), 216 (100), 287 (59), 188 (36), 217 (20), 172 (14). Anal. ($C_{19}H_{25}FN_2O$) C, H, N.

(*S*)-(−)-8-(Dipropylamino)-4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*S*-(−)-21). In a manner similar to that for the racemic material, (*S*)-(−)-(4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (*S*-(−)-**20**) (63 mg, 0.22 mmol) was converted to a crude product (60 mg, 86%), which was purified on a silica gel column (methanol) to yield 55 mg (79%) of pure product. For biological and analytical purposes, the fumarate salt was prepared in methanol and recrystallized from methanol/diethyl ether: mp 172–174 °C (fumarate); $[\alpha]^{20}_D$ −71.1° (c 1.0, methanol). Anal. ($C_{18}H_{25}FN_2 \cdot C_2H_2O_2 \cdot {}^1/_2H_2O$) C, H,* N; H calcd 7.36, found 6.8.

(*R*)-(+)-8-(Dipropylamino)-4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*R*-(+)-21). In a manner similar to that for the racemic material, (*R*)-(+)-(4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (*R*-(+)-**20**) (37 mg, 0.13 mmol) was converted to a crude product (44 mg, >100%), which was purified on a silica gel column (methanol) to yield 30 mg (73%) of pure product. For biological and analytical purposes, the fumarate salt was prepared in methanol and recrystallized from methanol/diethyl ether: mp 173–175 °C (fumarate); $[\alpha]^{20}_D$ +73.0° (c = 1.0, methanol). Anal. ($C_{18}H_{25}FN_2 \cdot C_2H_2O_2 \cdot {}^1/_2H_2O$) C, H, N.

8-(Dipropylamino)-4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbonitrile (22). To an ice-cooled solution of (4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (**20**) (108 mg, 0.37 mmol) in acetonitrile (5 mL) was added a solution of chlorosulfonyl isocyanate (64 μL, 72 mg, 0.50 mmol) in acetonitrile (0.5 mL) under argon. After 20 min, dimethylformamide (31 μL, 33 mg, 0.45 mmol) was added. After additional stirring for 1 h, the mixture was poured onto ice, and 32% ammonia was added dropwise until the mixture became basic. Extraction three times with dichloromethane and two times with ethyl acetate afforded an opalescent organic solution/suspension which was evaporated. The residue was redissolved in methanol, inorganic salts were filtered off, and the solution was evaporated again to yield 99 mg (85 %) of a product, which was further purified on a silica gel column using methanol as eluant: mp 222–225 °C (free base); ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$) δ 1.0 (t, 6H), 1.75 (sxt, 2H), 1.85 (m, 1H), 2.35 (br d, 1H), 2.7–3.4 (m, 4H), 3.6 (dd, 1H), 6.75 (d, J = 11.2 Hz, 1H), 7.8 (s, 1H); MS *m/e* 313 (M^+, 6), 213 (100), 284 (51), 173 (16), 197 (15). Anal. ($C_{19}H_{24}FN_3$) C, H, N.

1-[8-(Dipropylamino)-4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]propan-1-one (23). A mixture of (4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (**20**) (45 mg, 0.16 mmol) and phosphorus oxychloride (50 μL, 30.4 mg, 0.20 mmol) in *N*,*N*-dimethylpropionamide (200 μL) was heated to 80 °C and stirred for 3 h. After cooling to ambient temperature 15% sodium hydroxide was cautiously added to make the mixture basic. The reaction mixture was then heated again at 80 °C for 10 min, diluted with water, and extracted three times with ethyl acetate. The combined organic phases were dried (magnesium sulfate), filtered, and evaporated to a residue of 30 mg that was purified on a silica gel column to yield 22 mg (40%) of pure product. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp 205–207 °C (fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.25 (t, 3H), 1.50 (d of sxt, 4H), 1.70 (m, 1H), 2.02 (br d, 1H), 2.58 (m, 4H), 2.8–3.05 (m (incl. dq, 2H), 5H), 3.05–3.2 (m, 1H), 3.4 (dd, 1H), 6.74 (d, J = 11.2 Hz, 1H), 7.80 (s, 1H), 9.15 (br s, 1H); MS *m/e* 344 (M^+, 22), 315 (100), 244 (90), 57 (30), 186 (13). Anal. ($C_{21}H_{29}FN_2O \cdot C_2H_2O_2 \cdot {}^1/_2H_2O$) C, H, N.

(4-Fluoro-1-propyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (24). To a solution of 1-[8-(dipropylamino)-4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]propan-1-one (**23**) (30 mg, 0.087 mmol) in diethyl ether was added 95 mg of lithium aluminum hydride. The mixture was stirred for 2 h at room temperature and then the reaction quenched (95 μL of water, 95 μL of 15% sodium hydroxide, and 285 μL of water). After 10 min the precipitated aluminum salts were filtered off, and the resulting solution was evaporated to yield a residue of 60 mg. The material was purified on a silica gel column first using methanol as eluant and then with ethyl acetate in a second column. Pure material (14 mg, 45%) was

recovered, which was converted into its fumarate salt and recrystallized from methanol/diethyl ether: mp 179–182 °C (fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.03 (t, 3H), 1.50 (sxt, 4H), 1.70 (m, 3H), 2.05 (br d, 1H), 2.55 (t, 4H), 2.8–3.1 (m, 6H), 3.40 (br d, J = 10.3 Hz, 1H), 6.60 (d, J = 11.5 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 8.05 (br s, 1H). Anal. ($C_{21}H_{31}FN_2 \cdot C_4H_4O_4 \cdot {}^1/_4H_2O$) C, H, N.

(4-Fluoro-3-methyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (25). Sodium hydride (25 mg, 0.54 mmol, 50% oil dispersion) was washed two times with hexane. Dry dimethylformamide (3 mL) was added followed by (4-fluoro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (**20**) (114 mg, 0.40 mmol). After stirring for 20 min at ambient temperature, iodomethane (71 mg, 0.50 mmol) was added over a 5 min period, and the reaction mixture was stirred for 1 h. The mixture was poured onto diethyl ether/saturated sodium carbonate and extracted two additional times (diethyl ether). The combined organic extracts were dried (magnesium sulfate), filtered, and concentrated to 60 mg (48%) of the desired product. The fumarate salt was prepared in methanol and recrystallized from methanol/diethyl ether for analytical purposes: mp 138–140 °C (fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.51 (sixt, 4H), 1.65 (m, 1H), 2.05 (br d, 1H), 2.52 (t, 4H), 2.70–3.12 (m, 5H), 3.93 (d, J = 1.7 Hz, 3H), 6.40 (t, J = 2.7 Hz, 1H), 6.58 (d, J = 13.2 Hz, 1H), 6.93 (d, J = 2.9 Hz, 1H); MS m/e 302 (M^+, 21), 202 (100), 175 (45), 273 (35), 186 (13). Anal. ($C_{19}H_{27}FN_2 \cdot C_4H_4O_4 \cdot {}^1/_2H_2O$) C, H, N.

8-(Dipropylamino)-4-fluoro-3-methyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (26). In a similar manner as described for **21**, (4-fluoro-3-methyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (**25**) (61 mg, 0.20 mmol) was converted to a crude product (40 mg, 0.12 mmol) which was purified on a silica gel column (methanol) to yield 25 mg (37%) of pure compound. The fumarate salt was prepared as described earlier: mp 165–170 °C (fumarate); MS m/e 330 (M^+, 8), 230 (100), 301 (53), 202 (30), 231 (26), 186 (14). Anal. ($C_{20}H_{27}FN_2O \cdot C_4H_4O_4 \cdot 2H_2O$) C, H, N.

1-[8-(Dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]-2,2,2-trifluoroethanone (27). To a solution of 6,7,8,9-tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (**4**) (47 mg, 0.17 mmol) in *N*,*N*-dimethylformamide (117 mL) was very slowly added trifluoroacetic acid anhydride (29.1 μL, 0.21 mmol, 1.2 equiv), and the mixture was stirred at room temperature for 31 h. After 7 h, more trifluoroacetic acid anhydride (30 μL) was added. Water was added, and the product was extracted with diethyl ether, dried (sodium sulfate), and evaporated. The crude product (45 mg, 0.123 mmol, 72% yield) was purified by chromatography on a silica gel column using dichloromethane and methanol (9:1) as eluants: mp 208–210 °C (fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (t, 6H), 1.8 (d, 4H), 2.0 (m, 1H), 2.4 (m, 1H), 2.7–3.0 (m, 2H), 3.1 (m, 4H), 3.3 (q, 2H), 3.9 (q, 1H), 6.8 (d, 1H), 7.3 (d, 1H), 7.9 (s, 1H), 11.2–11.8 (br s, 1H); MS m/e 367 (M + 1, 3), 366 (M^+, 14), 337 (100), 266 (91), 169 (75), 168 (31), 72 (26), 338 (19), 196 (15). Anal. ($C_{20}H_{25}F_3N_2O \cdot C_2H_2O_2 \cdot {}^1/_2H_2O$) C, H, N.

1-[8-(Dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]ethanone (28). A mixture of 6,7,8,9-tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (**4**) (108 mg, 0.40 mmol) and phosphorus oxychloride (200 μL, 121 mg, 0.80 mmol) in dimethylacetamide (300 μL) was stirred at 85 °C for 3 h. Sodium hydroxide (5 M, 3 mL) was cautiously added, and the resulting mixture was stirred at 85 °C for 10 min. After cooling, water and ethyl acetate were added. After separation the aqueous phase was extracted two additional times with ethyl acetate. The combined organic extracts were dried (magnesium sulfate), filtered, and evaporated to a residue of 140 mg, which was subjected to a silica gel column and eluted with methanol to yield 35 mg (28%) of the pure product. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp 169–171 °C (fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (sxt, 4H), 1.70 (oct, 1H), 2.05 (br d, 1H), 2.52 (s, 3H), 2.60 (t, 4H), 3.0 (m, 3H), 3.25 (dd, J = 9, 17 Hz, 1H), 3.60 (dd, J = 3.5, 17 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 7.77 (s, 1H), 9.8 (br s, 1H); MS m/e 312 (M^+, 27), 283 (100), 212 (78), 170 (35), 284 (20), 168 (18). Anal. ($C_{20}H_{28}N_2O \cdot C_4H_4O_4$) C, H, N.

[8-(Dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]phenylmethanone (29). A dry 25 mL flask equipped with a reflux condenser was charged with 6,7,8,9-tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (**4**) (1.0 g, 3.7 mmol), phosphorus oxychloride (0.41 mL, 4.55 mmol), and *N*,*N*-dimethylbenzamide (1.1 g, 7.40 mmol). The mixture was heated to 84 °C under argon for 2 h. Upon cooling to ambient temperature, the reaction mixture solidified. The reaction mixture was diluted with dichloromethane (100 mL) and washed well with 1 M sodium hydroxide. The basic layer was re-extracted with dichloromethane. The organic layers were combined, dried (sodium sulfate), filtered, and evaporated. The crude residue was purified by chromatography on a silica gel column with 40% ethyl acetate in hexane and then in 35% acetone in hexane with 1% triethylamine to give a yellow foam. The foam was dried under high vacuum at 69 °C for 2 days to give 354 mg (26%) of the free base as a yellow solid. The pale lavender HCl salt was prepared from ethereal HCl: mp 248–249 °C (HCl salt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.3 Hz, 6H), 1.46–1.36 (m, 4H), 1.72 (m, 1H), 2.00 (m, 1H), 2.37–2.48 (m, 4H), 2.95–3.03 (m, 4H), 3.15 (t, J = 13.2 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 3.0 Hz, 1H), 7.45 (dt, J = 1.4, 6.3 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.88 (d, J = 6.9 Hz, 2H). Anal. ($C_{25}H_{30}N_2O$) C, H, N.

2-[8-(Dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]-2-oxoacetamide (30). A solution of 6,7,8,9-tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (**4**) (569 mg, 2.1 mmol) in diethyl ether (10 mL) was cooled to 0 °C and treated dropwise with oxalyl chloride (0.35 mL, 4.0 mmol). After stirring at 0 °C for 20 min, the reaction mixture was warmed to room temperature for an additional 20 min and then treated with gaseous ammonia, resulting in the formation of a tan solid. After 20 min, the reaction mixture was diluted with saturated sodium hydrogen carbonate and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed once with brine, dried (magnesium sulfate), filtered, and concentrated to an orange solid. This material was recrystallized from ethyl acetate/hexane to give the desired material as a yellow solid (264 mg, 37%). This material was converted to the HCl salt by treatment with gaseous HCl as an ethereal solution to afford an off-white solid: mp 217–218 °C (free base); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (t, J = 7.2 Hz, 6H), 1.42 (sxt, J = 7.2 Hz, 4H), 1.55 (m, 1H), 1.91 (m, 1H), 2.50 (m, 4H), 2.90 (m, 3H), 3.09 (m, 1H), 3.55 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.65 (br s, 1H), 8.07 (br s, 1H), 8.28 (s, 1H), 12.04 (br s, 1H). Anal. ($C_{20}H_{27}N_3O_2 \cdot {}^1/_2H_2O$) C, H, N.

(*R*)-(+)-2-[8-(Dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]-2-oxoacetamide (*R*-(+)-30). (*R*)-(+)-6,7,8,9-Tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (*R*-(+)-**4**) (541 mg, 2.0 mmol) was converted to the oxoacetamide derivative under the conditions described above. The crude product was purified by recrystallization from ethyl acetate/hexane to give the desired material (400 mg, 59%) as a yellow solid. Physical data were identical to those of the racemate. This material was converted to its HCl salt by treatment with gaseous HCl as an ethereal solution: mp 296–298 °C dec (HCl salt); $[\alpha]^{20}_D$ +137° (c = 1.002, methanol). Anal. ($C_{20}H_{27}N_3O_2$) C, H, N.

(*S*)-(−)-2-[8-(Dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]-2-oxoacetamide (*S*-(−)-30). (*S*)-(+)-6,7,8,9-Tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (*S*-(+)-**4**) (541 mg, 2.0 mmol) was converted to the oxoacetamide derivative under the conditions described above. The crude product was purified by recrystallization from ethyl acetate/hexane to give the desired material (409 mg, 60%) as a yellow solid. Physical data were identical to those of the racemate. This material was converted to its HCl salt by treatment with gaseous HCl as an ethereal solution: mp 296–298 °C dec (HCl salt); $[\alpha]^{20}_D$ −131° (c = 0.846, methanol). Anal. ($C_{20}H_{27}N_3O_2 \cdot HCl \cdot {}^3/_4H_2O$) C, H, N.

2-[8-(Dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl]-*N*,*N*-diethyl-2-oxoacetamide (31). A solution of

6,7,8,9-tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (**4**) (213 mg, 0.79 mmol) in diethyl ether (2 mL) was cooled to 0 °C under nitrogen and treated dropwise with oxalyl chloride (0.20 mL, 2.4 mmol). Generation of a voluminous precipitate prompted the addition of more ether (2 mL). The reaction mixture was stirred at 0 °C for 30 min, at which point it was treated dropwise with a solution of diethylamine (0.8 mL, 8.0 mmol) in ether (1 mL). The resulting tan suspension was diluted with ether (ca. 4 mL) and stirred at room temperature for 2 h, whereupon the reaction mixture was partitioned between *tert*-butylmethyl ether (TBME) and saturated aqueous sodium hydrogen carbonate. The aqueous phase was extracted with TBME (3 × 20 mL), and the combined organic layers were washed once with water and once with brine, dried over magnesium sulfate, filtered, and concentrated to a thick golden syrup (423 mg). The majority of this material (403 mg) was chromatographed on 35 g of silica gel using 5% 3 M ammonia in methanol/dichloromethane (5:95) to give the desired pure product as a tan foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 6H), 1.14 (t, J = 7, 1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.56 (m, 4H), 1.71 (m, 1H), 2.10 (br d, J = 11 Hz, 1H), 2.67 (t, J = 7.1 Hz, 4H), 2.94 (m, 2H), 3.05 (m, 1H), 3.22 (dd, J = 17, 10 Hz, 1H), 3.31 (q, J = 7.1 Hz, 2H), 3.49 (q, J = 7.1 Hz, 2H), 3.80 (br dd, J = 17, 5 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.71 (s, 1H); FAB HRMS calcd 397.2729, found 397.2743.

8-(Dipropylamino)-1,3,6,7,8,9-hexahydrobenz[*e*]indol-2-one (32). To a solution of 6,7,8,9-tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (**4**) (400 mg, 1.5 mmol) in acetic acid (100 mL) and water (10 mL) was added a solution of pyridinium perbromide hydrobromide (560 mg, 1.8 mmol) in acetic acid (200 mL). The solution was heated to 80 °C for 5 h. After cooling, the mixture was evaporated to an aqueous residue, which was basified with 10% sodium carbonate and extracted three times with ethyl acetate. The combined organic extracts were dried (magnesium sulfate), filtered, and evaporated to a residue (400 mg), which was chromatographed on a silica gel column using ethyl acetate as eluant to give 250 mg (59%) of a yellow oil. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp 213–215 °C (fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (sxt, 4H), 1.60 (oct, 1H), 2.05 (br d, 1H), 2.48 (t, 4H), 2.5–3.1 (m, 5H), 3.35 (q, 2H), 6.65 (d, J = 7.9 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 8.75 (s, 1H); MS m/e 286 (M^+, 23), 257 (100), 186 (93), 158 (27), 72 (27). Anal. ($C_{18}H_{26}N_2O \cdot C_4H_4O_4 \cdot {}^1/_2H_2O$) C, H, N.

[1-[(Dimethylamino)methyl]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl]dipropylamine (33). A stock solution of Mannich reagent was prepared by mixing glacial acetic acid (40 mL), 1,4-dioxane (40 mL), 37% aqueous formaldehyde (3.2 mL), and 40% aqueous dimethylamine (4.8 mL) at 0 °C. A portion of this solution (2.5 mL) was transferred to a 4 mL Recti vial, cooled to 0 °C, and treated with a solution of 6,7,8,9-tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (**4**) (215 mg, 0.80 mmol) in dioxane (1 mL). The reaction mixture was stirred for 2 h at 0 °C and then poured into water (20 mL), whereupon the pH was adjusted to ca. 10 with 2 M sodium hydroxide and the resulting milky solution was extracted with dichloromethane (3 × 15 mL). The combined organic solutions were dried (magnesium sulfate), filtered, and concentrated to give a sticky, tan solid (242 mg), trituration of which with hexane provided the desired compound as a white, free flowing powder (109 mg, 42%). This material was converted to the bis-HCl salt (ether, HCl gas): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.6 Hz, 6H), 1.52 (m, 4H), 1.69 (br m, 1H), 2.02 (br m, 1H), 2.25 (s, 6H), 2.56 (m, 4H), 2.94 (m, 2H), 3.05 (br m, 2H), 3.38 (d, J = 13.7 Hz, 1H), 3.71 (d, J = 13.7 Hz, 1H), 3.74–3.68 (m, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 2.3 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.93 (br s, 1H). Anal. ($C_{21}H_{33}N_3 \cdot 2HCl \cdot {}^3/_4H_2O$) C, H, N.

(1-Methyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (34). To a suspension of 8-(dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (**5**) (28 mg, 0.10 mg) in diethyl ether (5 mL) was added lithium aluminum hydride (40 mg, 1.05 mmol), and the mixture was stirred at ambient temperature for 1 h. Water (40 μL), 15% sodium hydroxide (40 μL), and water (120 μL) were consecutively added, and the mixture was stirred for 10 min. The resulting precipitate was filtered off, and the solution was evaporated to a residue of 25 mg (94%) of pure product. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp 188–191 °C (fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (sxt, 4H), 1.65 (m, 1H), 2.05 (br s, 1H), 2.50 (s, 3H), 2.55 (t, 4H), 2.93 (dd, 2H), 3.0–3.2 (m, 2H), 3.52 (m, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.87 (s, 1H), 7.08 (d, J = 8.3 Hz, 1H), 7.9 (br s, 1H); MS m/e 284 (M^+, 50), 184 (100), 255 (68), 157 (36), 168 (11). Anal. ($C_{19}H_{28}N_2 \cdot C_4H_4O_4 \cdot 1H_2O$) C, H, N.

8-(Dipropylamino)-3-methyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (35). A mixture of sodium hydride (55% oil dispersion, 5 mg, 0.11 mmol) and 8-(dipropylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (**5**) (20 mg, 0.070 mmol) in dimethylformamide (3 mL) was stirred for 0.5 h at ambient temperature. Iodomethane (4.5 μL, 10 mg, 0.07 mmol) in dimethylformamide (1 mL) was added, and the resulting mixture was stirred for 2 h and then poured into water/ethyl acetate. After extracting two additional times, the combined organic extracts were dried (magnesium sulfate), filtered, and evaporated. The resulting residue was suspended in diethyl ether, and the solid material was filtered off. Evaporation of the filtrate yielded 14.7 mg (67%) of pure product, which was converted into its fumarate salt and recrystallized from methanol/diethyl ether: mp 84–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (sxt, 4H), 1.70 (quintet, 1H), 2.05 (br s, 1H), 2.55 (t, 4H), 2.9–3.15 (m, 5H), 3.50 (m, 1H), 3.82 (s, 3H), 7.07 (d, J = 8.3 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 10.22 (s, 1H); MS m/e 312 (M^+, 25), 283 (100), 212 (82), 184 (28), 213 (25), 284 (20). Anal. ($C_{20}H_{28}N_2O \cdot C_4H_4O_4 \cdot {}^1/_2H_2O$) C, H, N.

[1-(Methylsulfanyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)dipropylamine (36). To a solution of dimethyl disulfide (24.7 mL, 37.8 mg, 40 mmol) in dichloromethane (1 mL) was added sulfuryl chloride (32 mL, 54.5 mg, 40 mmol) at 0 °C. The resulting solution was stirred for 5 min and thereafter added to a solution of 6,7,8,9-tetrahydro-*N*,*N*-dipropyl-3*H*-benz[*e*]indol-8-amine (**4**) (108 mg, 0.40 mmol) in dichloromethane (5 mL) at 0 °C. After stirring for 2 h, water and ammonium hydroxide were added. The organic phase was washed with 10% sodium carbonate, dried (magnesium sulfate), filtered, and evaporated to a residue of 84 mg. This material was chromatographed on a silica gel column (methanol) to yield 60 mg of a material which was further purified on a HPLC semipreparative column (1% methanol and 4% ethyl acetate in hexane fraction) giving 28 mg (22%) of the pure compound. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp 176–179 °C (fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 6H), 1.55 (sxt, 4H), 1.7 (m, 1H), 2.08 (br d, 1H), 2.37 (s, 3H), 2.59 (t, 4H), 2.95 (dd, 2H), 3.0–3.2 (m, 2H), 4.05 (d, J = 12.5, 1H), 6.93 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 8.25 (br s, 1H); MS m/e 316 (M^+, 49), 287 (100), 216 (81), 169 (29), 167 (21). Anal. ($C_{19}H_{28}N_2S \cdot C_4H_4O_4 \cdot {}^1/_4H_2O$) C, H, N.

[1-(Methylsulfonyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl]dipropylamine (37). A solution of [1-(methylsulfanyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl]dipropylamine (**36**) (50 mg, 0.16 mmol), acetic acid (100 μL), and *m*-chloroperbenzoic acid (72 mg, 0.41 mmol) in dichloromethane (10 mL) was stirred at room temperature for 5 h. The progress in reaction was monitored on TLC. The mixture was washed with 3 M sodium hydroxide, dried (magnesium sulfate), filtered, and evaporated to a residue of 32 mg. This material was purified on a silica column using dichloromethane/methanol (9:1) as eluant, giving 9.0 mg (16%) of the pure material as a light oil and 10 mg of product contaminated with unidentified compounds: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 6H), 1.55 (sxt, 4H), 1.9 (m, 1H), 2.25 (br d, 1H), 2.8–3.1 (7), 3.21 (s, 3H), 3.2–3.35 (m, 1H), 4.0 (d, J = 12.1 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 8.25 (br s, 1H); MS m/e 348 (M^+, 13), 319 (100), 248 (37), 169 (29); FAB HRMS calcd 348.1861, found 348.1871.

X-ray Analysis of *S*-(−)-20 Ditoluoyltartaric Acid Salt. The salts obtained in the resolution step of **2b** were used, and a crystal with the dimensions 0.36 × 0.36 × 0.12 mm was

Table 4. Crystal Data for *S*-(−)-**20**

formula	$C_{18}H_{25}FN_2{\cdot}C_{20}H_{18}O_8$
space group	$P2_1$
a (Å)	8.6650 (8)
b (Å)	13.8816 (15)
c (Å)	29.956 (5)
β (deg)	97.760
d_{calc} (g cm^{-3})	1.255
μ (cm^{-1})	7.2
V (Å^3)	3570
Z	4

selected for data collection with an Enraf-Nonius CAD4F-11 diffractometer. The angular settings of 25 reflections ($25° < \theta < 52°$) were measured to calculate the lattice parameters, cf. Table 5 (supplementary material) for crystal data. Intensity data for one unique set of reflections with $\theta = 75°$ ($-10 \le h \ge 10$, $0 \ge k \ge 16$, $0 \ge l \ge 37$) were collected by the $\theta/2\theta$ scan method using monochromatized CuKα radiation. Three intensity control reflections, which were measured every 2 h, indicated no significant decay. A total of 7667 reflections were recorded, and of these, 5586 reflections with $I > 2.5\sigma(I)$ were observed. All intensities were corrected for Lorentz and polarization effects but not for absorption or extinction. The structure was solved by direct methods with MITHRIL,[42] which provided the non-hydrogen atom positions. Remaining hydrogen atoms were included at calculated positions except those H atoms connected to methyl carbon or oxygen atoms, which were omitted. Refinement was carried out by the full-matrix least-squares method using anisotroipic temperature factor equal to the U_{eq} value of the parent atom. The hydrogen atom parameters were not refined. The absolute configuration of (−)-**21** was established from the known configuration of the counterion. After refinement the residuals were $R = 0.057$ and $R_w = 0.070$ (unit weights, $S = 0.156$, $\Delta/\sigma < 0.01$, $-0.21 < \Delta\varrho < 0.31$ e Å^{-3}). All calculations have been performed using mainly the program NRCVAX.[43] The molecular conformation is shown in Figure 3. Crystal data are shown in Table 4.

Computational Methods. The variables generated for the principal component analysis (PCA) were extracted from molecular mechanics calculations using PCModel[41] (MMX) and from semiempirical calculations using HyperChem[19] (PM3). The PCA was performed using SIMCA.[44] Torsional drivers were performed using PCMODEL.[41]

Pharmacology. Animals. Male rats used in the biochemical and motor activity experiments were of the Sprague–Dawley strain (ALAB, Sollentuna, Sweden), weighing 200–300 g. The rats were kept 5/cage with free access to water and food, for at least 1 week from arrival until used in the experiments.

Materials. All substances to be tested were dissolved in 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 solution. Injection volumes were 5 mL/kg, and all solutions had neutral pH at the time of injection (except for the solutions of reserpine, pH ≈ 4).

Biochemistry. 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.[45,46] Separate dose–response curves based on four to six dose levels ($n = 4$) for each substance (sc administration) and each brain area were constructed. From these curves, the dose of the drug yielding a half-maximal decrease (ED_{50} value) of the DOPA and 5-HTP levels (Table 2) was determined. The maximal effect, expressed as percent of controls, for DOPA was normally limbic system = −65%, striatum = −80%, and hemispheres = −50% and for 5-HTP was limbic system, striatum, and hemispheres = −50%. Control values for 5-HTP were (ng/g, mean ± SEM, $n = 10$) limbic system = 192 ± 18, striatum = 129 ± 14, and hemispheres = 131 ± 14. Control values for DOPA were (ng/g, mean ± SEM, $n = 10$) limbic system = 808 ± 56, striatum = 3653 ± 222, and hemispheres = 156 ± 11. The dose–response curves were obtained by nonlinear curve fitting to a sigmoidal function according to a previously described method.[7]

Binding Assays. Competition binding experiments employed 11 drug concentrations in duplicate. Radioligands used were [^{3}H]U86170[47] (62 Ci/mmol, 2 nM) for D_2-dopamine, [^{3}H]-spiperone (107 Ci/mmol, 0.6 nM) for D_3-dopamine, [^{3}H]-8-OH-DPAT (85 Ci/mmol, 1.2 nM) for 5-HT_{1A}-serotonin, and [^{3}H]-serotonin (10 Ci/mmol, 5 nM) for 5-$HT_{1D\alpha/\beta}$-serotonin receptors. Specific binding (80–90% of total) was determined with 3 μM haloperidol (D_2 and D_3 receptors), 3 μM lizuride (5-HT_{1A} receptors), or 3 μM 5-HT (5-HT_{1D} receptors). Cloned mammalian receptors expressed in CHO-K1 cells were used in each case.[48–51] Buffers used were 20 mM HEPES, 10 mM $MgSO_4$, pH 7.4, for D_2-dopamine; 20 mM HEPES, 10 mM $MgSO_4$, 150 mM NaCl, 1 mM EDTA, pH 7.4, for D_3-dopamine; 50 mM Tris, 5 mM $MgCl_2$, pH 7.4, for 5-HT_{1A}; and the same containing 0.1% ascorbic acid for 5-HT_{1D} receptors. Binding reactions were prepared by the addition of 50 μL of test compound dilution, 50 μL of radioligand, and 800 μL of membrane homogenate. The reaction mixtures were incubated at room temperature for 1 h (those containing serotonin were protected from light) in 96-well assay plates. Binding was terminated by filtration with a Tom Tec 96-well harvester. Counting was with a 1205 β-plate (Wallac) using MeltiLex G/HS (Wallac) scintillant. IC_{50} values were estimated by fitting the data to a one-site model by nonlinear least-squares minimization:

$$Y = B\frac{(T - B)}{(1 + 10)^{X - \log(IC_{50})}}$$

where Y is the mean specific counts associated with drug concentration X and T and B represent the specific counts about the top and bottom of the competition curve, respectively. K_i values were calculated with the Cheng–Prushoff equation.[52]

Absolute Oral Bioavailability of Compound 22. Blood plasma levels were analyzed by gas chromatography (Hewlett Packard)/mass spectrometry (VG Trio II). Male Sprague–Dawley rats treated orally with drug were starved 18 h before the experiment. The blood samples (100–150 μL) were collected at various time intervals up to 10 h after drug injection.

The weighed samples were diluted with 1 mL of water, and the internal standard 8-methoxy-2-[(dicyclopropylmethyl)-amino]-1,2,3,4-tetrahydronaphthalene[53] (25 ng) was added. The pH was adjusted to 11.0 by addition of saturated sodium carbonate (50 μL). After mixing, the samples were extracted with dichloromethane (4 mL) by shaking for 30 min. The organic layer was transferred to a smaller tube and evaporated to dryness under a stream of nitrogen. The reagent was evaporated under nitrogen, and the sample was redissolved in 40 μL of toluene for GC–MS analysis. A standard curve over the range 1–1000 pmol/mL was prepared by adding appropriate amounts of 1 standard to blank blood samples. Gas chromatography was performed on a cross-linked PS 264 capillary column (15 m × 0.25 mm) with 2 μL samples being injected in the splitless mode. The GC temperature was held at 90 °C for 1 min following injection and then increased by 30 °C/min to a final temperature of 290 °C. The absolute oral bioavailability of the compound was assessed by comparing the areas under the curves (AUC), for po ($n = 5$) and iv ($n = 3$) administration, in graphs where the blood concentrations of the compound were plotted against time.

Acknowledgment. The authors wish to express their gratitude to Maria Gullme and Anna Sandahl for skilful chemistry assistance and to Kirsten Sönniksen, Lena Wollter, Arja Schedwin, Marianne Thorngren, Marie-Charlotte Eriksson, Max Lundmark, and Anna-Carin Jansson for the competent *in vivo* experiment performance. Financial support from The Upjohn Co. is gratefully acknowledged.

Note added in Proof. Some of the compounds in this series have, when tested, responded positively in the Ames test, indicating a mutagenic potential (Mayo, J. D.; Aaron, C. S. The Upjohn Co., Kalamazoo, MI. Personal communication.)

Supplementary Material Available: ^{13}C NMR data, elemental analysis protocol, crystal data, positional and thermal parameters, bond lengths, and bond angles (17 pages); tables of observed and calculated structure factors (25 pages). Ordering information is given on any current masthead page.

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JM940680E