Further Characterization of Structural Requirements for Ligands at the Dopamine D₂ and D₃ Receptor: Exploring the Thiophene Moiety

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The present study describes the synthesis and in vitro pharmacology of a novel series of dopaminergic agents in which the classical phenylethylamine pharmacophore is replaced by a thienylethylamine moiety. In general, the novel compounds showed a moderate affinity for the dopamine (DA) D₂ and D₃ receptors. When the thienylethylamine moiety is fixed in a rigid system, the affinity for the DA receptor is significantly increased. However, in the tricyclic hexahydrothianaphthoxazine structure, the affinity for the DA receptors is diminished.

Introduction

Recent advances in molecular biology have established the existence of two families of dopamine receptors: a D₂-group comprising D₂, D₃, and D₄ receptors and a D₁-group incorporating D₁ and D₅ receptors.[1,2] Dopamine (DA) is a major neurotransmitter in the central nervous system. Receptors for this catecholamine are of considerable interest, as they are the principal target for drugs employed in the treatment of neuropsychiatric disorders, such as schizophrenia, drug dependence, and Parkinson's disease. For that reason, dopaminergic ligands have attracted considerable attention.[3–5]

DA receptor agonist activities can be found in several classes of compounds, including 2-phenylethylamines, aporphines, 2-aminotetralins, naphthoxazines, and ergoline derivatives. Dopamine, and most of the known DA receptor agonists, bind with a higher affinity to the DA D₃ than to the DA D₂ receptor. Due to the close homology between the DA D₂ and D₃ receptors, especially in the TM domains (∼80%), it is difficult to predict DA D₂ versus DA D₃ receptor selectivity based on receptor models. Malmberg et al.[6] suggested that the observed DA D₃ selectivity may not be due to a single specific interaction but, rather, to a small difference in conformation between the D₃ and D₂ receptors.

McDermed et al.[7] elegantly rationalized the heterochirality of the potent DA receptor agonists by suggesting a model in which different faces of the compound would interact with a putative three-point pharmacophore. An attractive feature of this model is that it allows a superposition of the pharmacophoric elements of several DA receptor agonists, such as the nitrogens, nitrogen lone pairs, oxygens, and aromatic rings. In addition, the presence of two lipophilic sites which bind the *N*-alkyl groups has been postulated.[8] Wikström et al.[9] have shown with a series of octahydrobenzo[*f*]-quinolines, using a pharmacological in vivo model measuring DA D₂ activity, that one of the *N*-alkyl binding sites can only tolerate N-substituents equal to an *n*-propyl. Seiler and Markstein[10] conclude that this space-limited accessory binding site, which they call the "small *N*-alkyl binding site", exists in both main groups of the DA receptors.

For a more extensive exploitation of this theory, we synthesized some derivatives of the potent DA D₂/D₃ agonist PHNO **1a**.[11,12] According to the Wikström/Seiler modification of McDermed's model, N-substituents larger than *n*-propyl should produce compounds which are inactive at the DA D₂/D₃ receptors, while the steric requirements for an R group on the 2-position should be less critical.

The in vitro pharmacology data of the naphthoxazines (Table 1) confirmed that an N-substituent should not be larger than an *n*-propyl, and that there is more structural freedom for a 2-substituent. However, a thienylethyl substituent on the nitrogen (**1c**) gave a compound with a significantly higher affinity for the DA D₃ receptor than for the phenylethyl analogue **1b**. We speculated about the reason for the increased affinity for the D3 receptor and hypothesized that the dopaminergic pharmacophore of compound **1c** is the thienylethylamine moiety (pharmacophore **2**, Chart 1) and not the 3-OH-phenylethylamine moiety (pharmacophore **1**, Chart 1). The possibility of an interaction of the thienylethylamine moiety with additional parts of the receptor cannot be ruled out entirely. To test the hypothesis, the thienylethylamines **3** and **4** were synthesized and tested in vitro (Chart 2).

It has been known for a long time that the 2-aminotetralin (2-amino-1,2,3,4-tetrahydronaphthalene) structure is pharmacologically valuable. The 2-aminotetralin system has proven to be a useful structural base for dopaminergic, serotonergic, and adrenergic ligands, as well as for compounds that interact with melatonin receptors.[13,14]

Some of these compounds have been studied by several research groups to elucidate their SAR for DA receptors.[8–10,15–19] Initially, these studies identified *S*-

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Chart 1. Structures of Some Dopaminergic Ligands

1a. R = CH₃ (*trans*-PHNO)
b. = phenyl (*trans*)
c. = 2-thienyl (*trans*)

2 (*trans*)

— Pharmacophore 1
— Pharmacophore 2
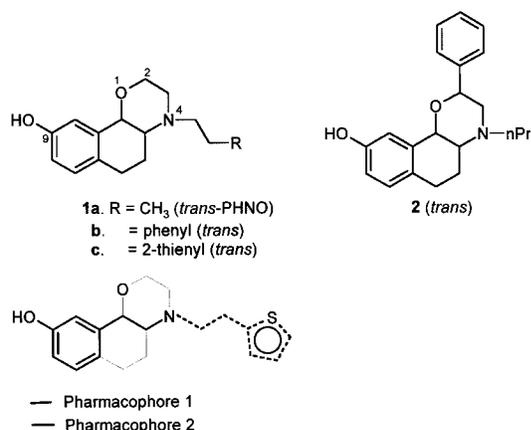
Chart 2. Chemical Structures of Some Thienylethylamines

3　　　　**4**
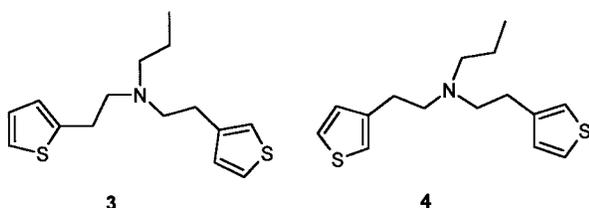
Chart 3. Chemical Structures of Some 2-Aminotetralins and Analogues

S-(−)-**5**

R-(+)-**6**

S-(−)-**7**

8

9
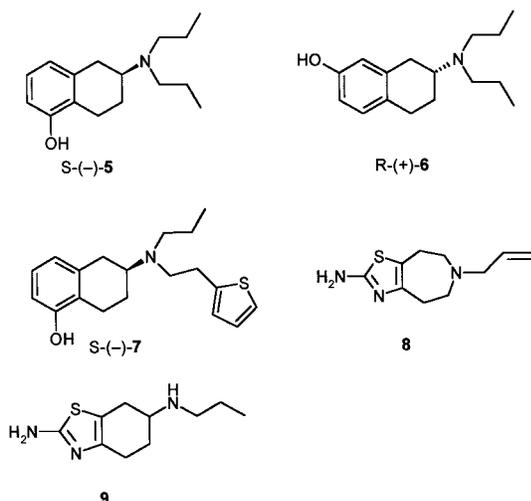
(−)-5-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin (*S*-(−)-5-OH-DPAT or *S*-(−)-**5**) as the most potent monohydroxy 2-aminotetralin.[8,10,15] Later, *S*-(−)-5-hydroxy-2-(*N*-*n*-propyl-*N*-2-thienylethylamino)tetralin (*S*-(−)-*N*-0437 or *S*-(−)-**7**) was found to be an even more potent DA receptor agonist.[19] Moreover, *R*-(+)-7-hydroxy-2-(*N,N*-di-*n*-propylamino)tetralin (*R*-(+)-7-OH-DPAT or *R*-(+)-**6**) was later shown to have a preference for the DA D₃ receptor subtype (Chart 3).[20,21]

The clinical utility of catechol- and phenol-containing drugs has been limited due to their low oral bioavailability and short duration of action. The catechol and phenol rings provide optimal sites for glucuronidation. Thus, for many years, emphasis has been focused on the identification of bioisosteric replacements of catechols and phenols. The idea that neither catecholic nor phenolic hydroxyl groups are an absolute requirement

Chart 4. Chemical Structures of Novel Thiophene Analogues of 2-Aminotetralins and Hexahydronaphthoxazines

10　　　　**11**

12　　　　**13**

14　　　　**15**

Scheme 1[a]

trans-**16**

trans-**17a**) Ar = phenyl
trans-**17b**) Ar = 2-thienyl

trans-**1b**) Ar = phenyl
trans-**1c**) Ar = 2-thienyl
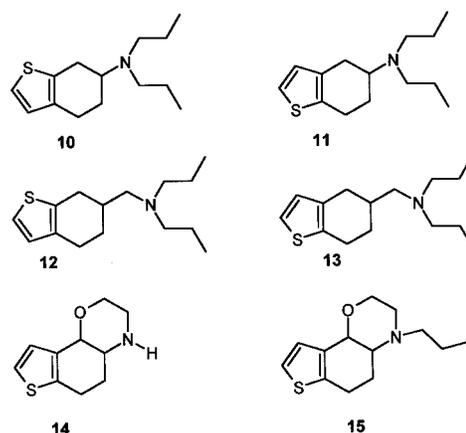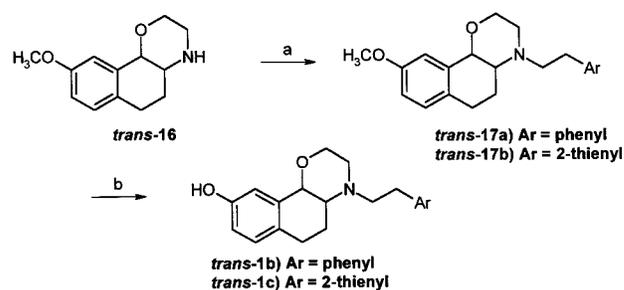
[a] Reagents: (a) C₆H₅CH₂CH₂Br, K₂CO₃, DMF or 2-thienyl acetic acid, (CH₃)₃N·BH₃, xylene; (b) BBr₃, CH₂Cl₂.

for potent dopaminergic activity was presented by Andén et al.,[22] who showed that the aminothiazolazepine derivative BHT920 (**8**) is a DA autoreceptor agonist, as well as an α₂-adrenoceptor agonist. Pramipexole (**9**), a benzothiazole analogue of the 2-aminotetralins, was found to be a potent DA receptor ligand with both DA D₂ and D₃ receptor stimulating properties (Chart 3). It is presently on the market for the treatment of Parkinson's disease.[23−25]

Since it was found that compounds with a thienylethylamine moiety have an affinity for the dopamine receptor, we were interested in the effect of the replacement of the phenol in 2-aminotetralins and hexahydronaphthoxazines with a thiophene moiety. Therefore, thiophene analogues of the 2-aminotetralins and hexahydronaphthoxazines, **10**−**15**, were synthesized (Chart 4). All the compounds synthesized were tested in vitro for their affinity at the DA D₂L and D₃ receptors. The derivatives with interesting properties were further investigated for their in vivo dopaminergic activity and bioavailability using the microdialysis technique in freely moving rats.[26]

Chemistry

The *trans*-*N*-arylalkyl substituted hexahydronaphthoxazines **1b** and **1c** were synthesized from the *trans*-9-methoxy secondary amine **16** either by N-alkylation with the appropriate arylethyl halide or by reductive alkylation.[11] The cleavage of the methoxy ethers to phenols was achieved with BBr₃ under N₂ (Scheme 1).

The synthesis of 2-phenyl-*N*-*n*-propylnaphthoxazine is outlined in Scheme 2. The racemic *trans*-amino

Scheme 2[a]
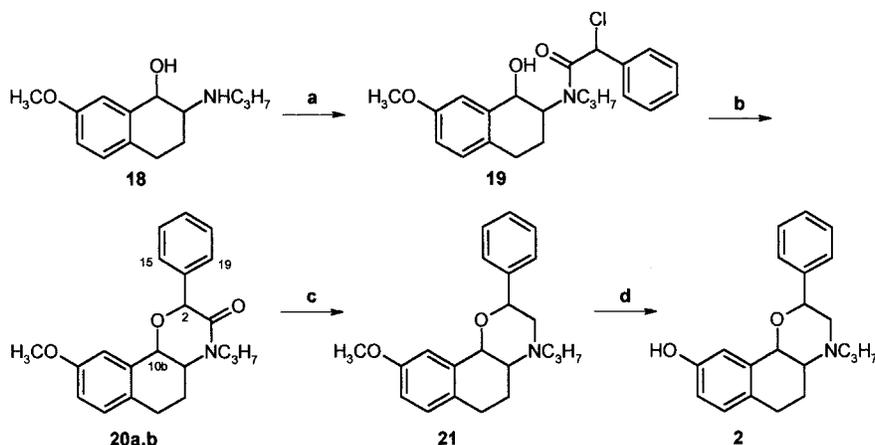
[a] Reagents: (a) PhCHClCOCl, NaOH, CH$_2$Cl$_2$; (b) NaOH, 2-propanol; (c) BH$_3$·Me$_2$S, THF; (d) BBr$_3$, CH$_2$Cl$_2$.

Scheme 3[a]
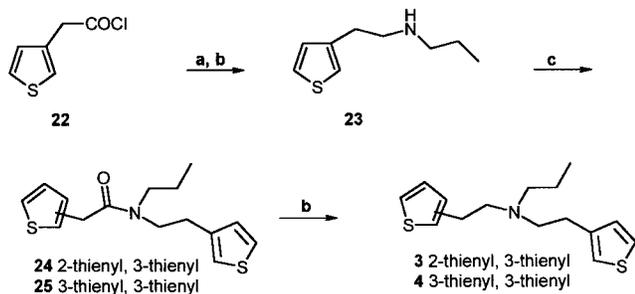
[a] Reagents: (a) C$_3$H$_7$NH$_2$, CH$_2$Cl$_2$; (b) BH$_3$·Me$_2$S, THF; (c) 2- or 3-thienylacetyl chloride, CH$_2$Cl$_2$, Et$_3$N.

Scheme 4[a]

[a] Reagents: (a) ClMgCH$_2$SiMe$_3$, Ni(PPh$_3$)$_2$Cl$_2$, Et$_2$O; (b) CH$_3$I, CH$_3$CN; (c) CH$_2$=CHCO$_2$CH$_3$, TBAF, CH$_3$CN; (d) NaOH; (e) (1) DPPA, Et$_3$N, dioxane; (2) HCl, dioxane, 120 °C; (f) C$_3$H$_7$I, K$_2$CO$_3$, DMF; (g) SiO$_2$ column chromatography, EtOAc:hexane = 1:9.

alcohol **18** was acylated with 2-chloro-2-phenylacetyl chloride to afford a mixture of diastereomeric *trans*-amido alcohols. Cyclization of the amido alcohol **19** was achieved with NaOH in 2-propanol, affording the mixture of *trans*-lactams **20a** and **20b** with the 2-phenyl ring in the equatorial or axial position.

The 2-(axial)phenyl *trans*-lactam and the 2-(equatorial)phenyl *trans*-lactam could be separated by column chromatography. NOESY experiments show that the fast-eluting compound has an interaction between the protons on C10b and C15/C19; hence, this is the compound with the phenyl ring in the axial position. The slow-eluting compound shows an interaction between the protons on C10b and C2, indicating that the compound has the phenyl ring in the equatorial position. The 2-equatorial-phenyl isomer was used for the next reaction. After reduction of the amide with the BH$_3$·Me$_2$S complex, the final step was demethylation, which was achieved by applying BBr$_3$ to give the final product **2**.

The thienylethylamines **3** and **4** were synthesized according to Scheme 3. The secondary amine **23** was acylated with 2- or 3-thienylacetyl chloride. The ^{1}H- and ^{13}C-NMR spectra of the amides **24** and **25** showed nonequivalency for the aliphatic hydrogen and carbon atoms, indicating a partial double-bond character. The resulting amides were reduced with the BH$_3$·Me$_2$S complex.

The synthesis of the tetrahydrobenzo[*b*]thiophenes is outlined in Scheme 4. A Grignard reaction of **26** with ClMgCH$_2$SiMe$_3$ followed by quaternization with methyl iodide gave the 3-(trimethylammoniummethyl)-2-(tri-

methylsilylmethyl)thiophene **28**.[27] Treatment of **28** with *n*-tetrabutylammonium fluoride (TBAF) led to the formation of 2,3-dimethylene-2,3-dihydrothiophene. This unstable intermediate was captured in a Diels−Alder [4 + 2] cycloaddition reaction with methyl acrylate as the dienophile. Hydrolysis of the mixture of esters gave the carboxylic acids **30a** and **30b** in good yield. A Curtius rearrangement gave the mixture of the amines **31a** and **31b**.[27] Only after conversion into the tertiary amines of **10** and **11** was it possible to separate the mixture of regioisomers on a SiO$_2$ column.

The methyleneaminotetrahydrobenzo[*b*]thiophenes **12** and **13** were synthesized from the corresponding carboxylic acids **30a** and **30b** in three steps by standard chemistry (Scheme 5). Again, the two isomers could be separated on a SiO$_2$ column after their conversion to the tertiary amines.

The hexahydrothianaphthoxazines **14** and **15** were synthesized from the commercially available ketone **34**, which was readily converted into the tosyloxime **36** (Scheme 6). Neber rearrangement of **36** with potassium *tert*-butoxide afforded the desired amino ketone **37**. The amino ketone **37** was readily acylated with chloroacetyl chloride. Reduction of the keto-chloroacetamide **38** with sodium borohydride gave only the trans isomer. The proton on C1 gave a doublet at δ 4.6 ppm with a coupling constant of 7.2 Hz, indicating a diaxial cou-

Scheme 5[a]
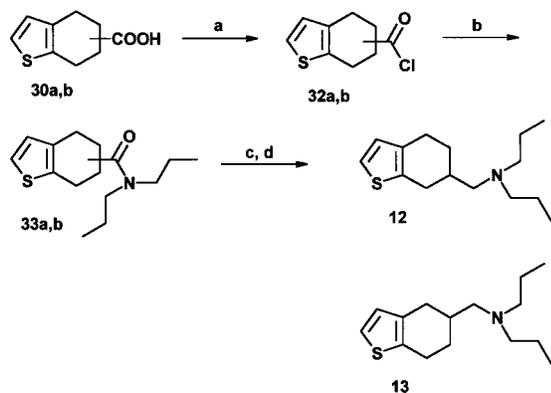
[a] Reagents: (a) oxalyl chloride, CH_2Cl_2; (b) $(C_3H_7)_2NH$, Et_3N, CH_2Cl_2; (c) $LiAlH_4$, THF; (d) SiO_2 column chromatography, $CH_2Cl_2:MeOH = 20:1$.

pling. The cyclization of the alcohol-chloroacetamide **39** by means of 50% NaOH in 2-propanol at room temperature gave satisfactory yields of the lactam **40**, which was then reduced with $LiAlH_4$ to the oxazine **14**. Alkylation of the amine **14** with propyl iodide in DMF afforded the tertiary amine **15** in good yield.

Results and Discussion

The structural requirements for the N-substituents of dopaminergic 7- and 9-hydroxylated octahydrobenzo-[*f*]quinolines (OHB[*f*]Qs) and related compounds have been described previously.[9] In vivo biochemical and behavioral data demonstrated that the *n*-propyl group is optimal for dopaminergic activity. Larger N-substituents (e.g., *n*-butyl) for the 9-hydroxy-OHB[*f*]Qs gave a dramatic reduction in the potency of these compounds. The K_i values shown in Table 1 for the N-substituted 9-hydroxy-hexahydronaphthoxazines (9-OH-HNO) **1b** and **2** are in full agreement with the models of McDermed and Wikström.[7,9] According to these models, there is space available for a 2-substituent. Interestingly, however, the DA D_3 affinity of **1c** ($K_i = 83$ nM) showed that this compound does not fit these receptor models. This has led us to hypothesize that it is the thienylethylamine moiety of **1c** which confers the

Table 1. Receptor Binding Data of Various Dopaminergic Compounds

	K_i (nM)[a]	
compound no.	D_{2L} [^{3}H]N-0437	D_3 [^{3}H]spiperone
(+)-PHNO ((+)-**1a**)	6.24	0.21
(±)-**1b**	>3676	1566
(±)-**1c**	3676	83
(±)-**2**	375	12
3	1080	117
4	439	108
10	27	28
11	20	40
12	3107[b]	60
13	2037	247
14	>4780[b]	3000
15	630[b]	240
(−)-5-OH-DPAT (**5**)[5]	14	0.54
(+)-7-OH-DPAT (**6**)[5]	34	0.57
(±)-N-0437 (**7**)[5]	0.06	4.0

[a] K_i values are the means of two to six separate experiments, the results of which did not vary by more than 25%. [b] [^{3}H]NPA was used as a radiolabeled ligand.

dopaminergic D_3 properties to this compound. Several studies have shown that some transmembrane segments play an important role in the formation of the binding pocket of the DA receptors. This leads to the assumption that the protonated nitrogen of ligands interacts with Asp 114 (D_2) or Asp 110 (D_3) in TM 3 through a reinforced ionic bond (for review see ref 1). In the hydroxylated 2-aminotetralins and OHB[*f*]Qs, an additional hydrogen bond is formed from the phenolic hydrogen of the ligands to either Ser 193 (D_2) or Ser 192 (D_3) in TM 5.[6] If a thiophene ring utilizes the same interaction points as the phenol, it may be speculated that the sulfur atom in the thienylethyl substituent forms a hydrogen bond with the hydroxyl moiety of a Ser residue. Sulfur can only act as a hydrogen-bond acceptor, and consequently, this weaker interaction may provide an explanation for the lower affinity for the DA D_3 receptor of compound **1c** compared to that of compound **1a**.[28,29] An alternative explanation for the diminished affinity is the utilization of other interaction points of the receptor.

The in vitro pharmacology of compounds **3** and **4** possessing only the thienylethylamine moieties (Table

Scheme 6[a]
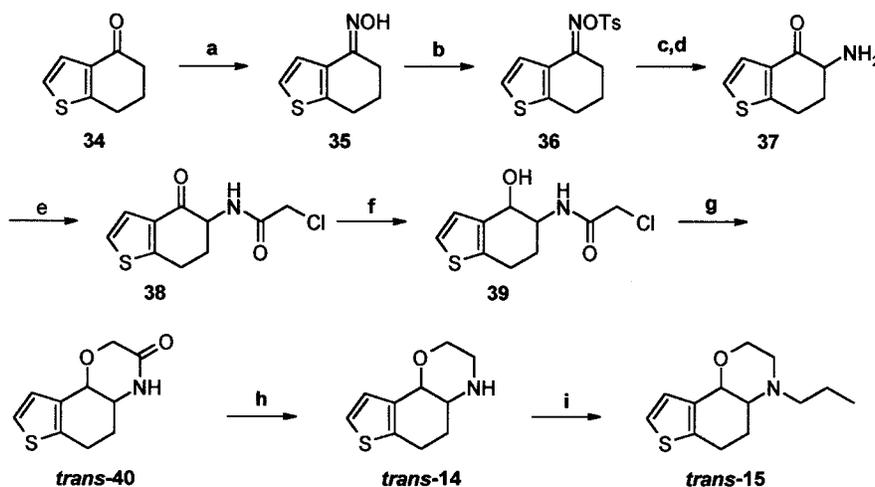
[a] Reagents: (a) $NH_2OH \cdot HCl$; (b) TsCl; (c) *t*-BuOK/EtOH; (d) HCl/H_2O; (e) $ClCH_2COCl$, NaOH, CH_2Cl_2; (f) $NaBH_4$; (g) NaOH; (h) $LiAlH_4$; (i) C_3H_7I, DMF, K_2CO_3.

1) showed that these compounds possess low to moderate affinity for the DA D_3 receptor, but it confirmed our assumption that a thienylethylamine moiety can act as a nonoptimal pharmacophore at the DA D_3 receptor.

The thiophene analogues of the 2-aminotetralins (**10** and **11**) have considerable affinity for the DA D_2 and D_3 receptors, but it is significantly lower than that for 5-OH-DPAT (Table 1). As stated earlier, one reason could be the less-tight hydrogen bonding of the sulfur atom. The results of compounds **10** and **11** confirmed the hypothesis that a thienylethylamine may act as a pharmacophore; moreover, compared to the thienylethylamines (**3**, **4**), the semirigid system increased the affinity for the DA receptor. Apparently, the near coplanar arrangement is favorable for higher DA agonist activity. This is in line with the higher potency of the hydroxylated 2-aminotetralin analogues compared to that of the phenylethylamines.[31,32] It is known from literature that hydroxylated 2-aminotetralins and hexahydronaphthoxazines are potent dopaminergic agonists, but their oral bioavailability is very low due to glucuronidation in the liver.[30] The use of microdialysis experiments in the rat allowed for the calculation of the relative oral bioavailabilities of the compounds **10**, **11**, and 5-OH-DPAT.[26] These data show that, although the affinities of the benzo[*b*]thiophenes (**10** and **11**) for the DA receptors are lower compared to those of 5-OH-DPAT, their relative oral bioavailability is higher. Compounds **10** and **11** showed relative oral bioavailabilities of 10% and >10%, respectively. The reference compound has a relative oral bioavailability of about 1%.[26] Therefore, the benzo[*b*]thiophenes are interesting lead compounds for further research.

Compounds **12** and **13** were synthesized to enlarge the distance between the nitrogen and sulfur atom. Compound **12** had no affinity for the DA D_2 receptor and only a moderate affinity for the DA D_3 receptor. The distance between the sulfur and nitrogen atoms of compounds **12** and **13** in an extended minimized conformation (using the computer program MacroModel) is between 5.7 and 6.7 Å, depending on the conformation of the methylene amino group. This distance is comparable with the distance between the hydroxyl group and the nitrogen atom in the 2-aminotetralins.

Although the distances between the sulfur and nitrogen atoms in the hexahydrothianaphthoxazines (**14** and **15**) are comparable with those in 5-(*N*-(di-*n*-propyl))-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene **11**, the introduction of a morpholine ring gave a dramatic decrease in the DA D_2 and D_3 receptor affinity.

In conclusion, bioisosteric replacement of a phenol by a thiophene moiety gave DA agonists with poorer affinity than the corresponding 2-aminotetralins. This loss in affinity is, however, partly compensated by a higher oral bioavailability of the tetrahydrobenzo[*b*]-thiophenes **10** and **11**.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries on an electrothermal digital melting-point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at 200 and 50.3 MHz, respectively, on a Varian Gemini 200 spectrometer. The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet),

m (multiplet), and dd (double doublet). Chemical shifts are given in δ units (ppm) and are relative to the solvent. Coupling constants are given in hertz (Hz). The spectra recorded were consistent with the proposed structures. IR spectra were obtained on an ATI-Mattson spectrometer. Elemental analyses were performed either by the Analytical Chemistry Section at Parke Davis (Ann Arbor, MI) or by the Microanalytical Department of the University of Groningen, and were within ±0.4% of the theoretical values, except where noted. All chemicals used were commercially available (Aldrich or Acros) and were used without further purification.

***trans*-9-Methoxy-4-(2-phenylethyl)-2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2*b*][1,4]oxazine (17a).** A solution of *trans*-9-methoxy-2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2*b*]-[1,4]oxazine (**16**) (0.42 g, 1.91 mmol), K_2CO_3 (1.5 g, 10.85 mmol), and 2-phenylethylbromide (0.39 g, 2.10 mol) in 15 mL of DMF was stirred for 15 h at 60 °C under an atmosphere of nitrogen. The reaction mixture was allowed to cool to room temperature, and then poured into water and extracted 3 times with 30 mL of diethyl ether. The combined organic phases were extracted several times with brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The residue was further purified by flash chromatography (SiO_2) using a mixture of CH_2Cl_2 and MeOH (25/1) as the eluent. After evaporation of the solvent, the yield was 0.39 g (63%) of **17a**, which was converted to the HCl salt: mp 239–241 °C; ^{1}H-NMR (CD_3OD, δ) 1.9–2.1 (m, 1H), 2.5–2.7 (m, 1H), 2.9–3.0 (m, 2H), 3.1–3.3 (m, 2H), 3.4–3.6 (m, 3H), 3.7–3.9 (m, 2H), 3.8 (s, 3H), 4.2–4.4 (m, 2H), 4.8 (d, 1H, $J = 9.3$ Hz), 6.9–7.0 (m, 1H), 7.0–7.2 (m, 2H), 7.3–7.5 (m, 5H); ^{13}C-NMR (CD_3OD, δ) 20.3, 24.7, 27.7, 49.7, 51.9, 53.3, 62.2, 62.7, 74.8, 108.4, 113.0, 124.7, 125.7, 127.4, 127.8, 133.4, 135.2, 156.9. Anal. ($C_{21}H_{25}NO_2 \cdot HCl$) C, H, N.

***trans*-9-Hydroxy-4-(2-phenylethyl)-2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2*b*][1,4]oxazine (1b).** To a cooled solution (−30 °C) of **17a**·HCl (0.22 g, 0.61 mmol) in 30 mL of dichloromethane was added a 1 M solution of BBr_3 in CH_2Cl_2 under an atmosphere of nitrogen. The reaction mixture was initially stirred for 1 h at this temperature, and then allowed to rise to room temperature, after which the reaction mixture was stirred for another 3 h. The reaction mixture was then poured into water that had been made alkaline by the addition of a solution of $NaHCO_3$. The separated organic layer was washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. Conversion to the HCl salt and recrystallization from acetonitrile yielded 0.12 g (51%) of **1b**: mp of the free base 173–176 °C; ^{1}H-NMR ($CDCl_3$, δ) 1.6–1.8 (m, 1H), 2.2–2.4 (m, 2H), 2.6–2.9 (m, 6H), 3.0–3.2 (m, 2H), 3.9–4.1 (m, 2H), 4.4 (d, 1H, $J = 9.7$ Hz), 6.6–6.8 (m, 1H), 6.9–7.0 (m, 2H), 7.2–7.4 (m, 5H); ^{13}C-NMR ($CDCl_3$, δ) 22.5, 25.6, 30.3, 50.7, 53.4, 60.9, 65.4, 77.1, 110.4, 113.2, 124.7, 125.2, 127.0, 127.2, 127.8, 152.8. Anal. ($C_{20}H_{23}$-$NO_2 \cdot 2HCl$) C, H, N.

***trans*-9-Methoxy-4-(2-thienylethyl)-2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2*b*][1,4]oxazine (17b).** To a solution of *trans*-9-methoxy-2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2*b*]-[1,4]oxazine (**16**) (0.5 g, 2.3 mmol) and trimethylamine borane complex (0.34 g, 4.6 mmol) in 30 mL of xylene was added 2-thienyl acetic acid (0.65 g, 4.5 mmol). The mixture was heated under N_2 and refluxed for 15 h. The mixture was poured into water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined organic layer was washed with $NaHCO_3$ solution and brine and dried over $MgSO_4$. Evaporation of the solvents yielded an oil which was converted to the HCl salt and recrystallized from ethanol to yield 0.46 g (62.3%) of **17b**: mp 195.5–197 °C; ^{1}H-NMR (CD_3OD, δ) 2.5–2.8 (m, 1H), 3.1–3.3 (m, 1H), 3.5–3.7 (m, 2H), 4.0–4.2 (m, 5H), 4.4–4.6 (m, 2H), 4.4 (s, 3H), 4.8–5.1 (m, 2H), 5.5 (d, 1H, $J = 9.5$ Hz), 7.5–7.6 (m, 1H), 7.7–7.9 (m, 2H), 8.1 (d, 1H, $J = 3.7$ Hz); ^{13}C-NMR (CD_3OD, δ) 20.9, 22.7, 25.4, 52.4, 53.8, 63.1, 63.3, 75.4, 109.1, 113.6, 124.0, 125.3, 125.6, 126.4, 128.4, 133.9, 137.3, 157.6. Anal. ($C_{19}H_{23}NO_2S \cdot HCl$) C, H, N.

***trans*-9-Hydroxy-4-(2-thienylethyl)-2,3,4a,5,6,10b-hexa-hydro-4*H*-naphth[1,2*b*][1,4]oxazine (1c).** Compound **1c** was prepared from the methoxy compound **17b** by essentially the same procedure as described for the preparation of **1b**. The yield was 65%. An analytical sample was recrystallized from ethanol diethyl ether to provide white crystals: mp of the free base 173−175 °C and of the HCl salt 231−234 °C; ^{1}H-NMR (CD$_3$OD, δ) 1.8−2.0 (m, 1H), 2.5−2.6 (m, 1H), 2.8−3.0 (m, 2H), 3.3−3.5 (m, 5H), 3.7−3.8 (m, 2H), 4.1−4.4 (m, 2H), 4.7 (d, 1H, J = 9.8 Hz), 6.6−6.7 (m, 1H), 6.9−7.1 (m, 4H), 7.3 (d, 1H, J = 4.9 Hz); ^{13}C-NMR (CDCl$_3$, δ) 20.3, 22.0, 24.6, 51.9, 54.0, 62.4, 62.8, 74.9, 109.9, 113.8, 122.9, 123.1, 124.7, 125.5, 127.3, 132.7, 136.1, 154.3. Anal. (C$_{18}$H$_{21}$NO$_2$S·HCl·^{1}/$_4$H$_2$O) C, H, N.

***trans*-9-Methoxy-2-phenyl-4-*N*-*n*-propyl-2,3,4a,5,6-tet-rahydro-4*H*-naphth[1,2*b*][1,4]oxazin-3-one (20a and 20b).** To a solution of **18** (1.14 g, 4.8 mmol) in 70 mL of dichloromethane was added NaOH (1.0 g) dissolved in 10 mL of water. The compound 2-chloro-2-phenyl acetyl chloride (1.0 g, 5.3 mmol) was dissolved in 10 mL of dichloromethane and slowly added. The reaction mixture was stirred at room temperature for 2 h. The mixture was then poured into 60 mL of water. The two layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with water and dried over Na$_2$SO$_4$. After filtration, the solvent was removed under reduced pressure to yield 1.7 g (91%) of oil as a mixture of diastereomers of compound **19** and a partly cyclized product: ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 3H, J = 7.3 Hz), 1.4−1.6 (m, 1H), 1.6−1.9 (m, 2H), 2.35−2.5 (m, 1H), 2.9−3.0 (m, 2H), 3.1−3.3 (m, 1H), 3.7−3.9 (m, 2H), 3.8 (s, 3H), 4.8 (d, 1H, J = 9.0 Hz), 5.4 (s, 1H), 6.7−6.8 (m, 1H), 7.0−7.15 (m, 2H), 7.3−7.4 (m, 3H), 7.5−7.6 (m, 2H); ^{13}C-NMR (CDCl$_3$, δ) 9.7, 19.7, 23.7, 25.5, 41.6, 53.9, 55.2, 75.2, 79.8, 108.3, 113.2, 124.6, 126.5, 126.7, 127.7, 134.0, 136.8, 156.9, 167.3. The compound was used without further purification.

To a solution of the chloroacetamide (**19**) in 200 mL of 2-propanol was added a solution of 1.2 g of NaOH in 2.4 mL of H$_2$O dropwise at rt. After being stirred for 5 h at room temperature, the mixture was neutralized with 1 N HCl. The solvents were evaporated, and the resulting residue was slurried in 200 mL of water and extracted with 4 × 25 mL of dichloromethane. The organic layer was washed with water, dried over Na$_2$SO$_4$, and then reduced to dryness. The residual solid was purified by column chromatography on silica gel 60 using a mixture of EtOAc and hexane (1/4) as the eluent, resulting in the separation of the two stereoisomers (**20a** and **20b**). Recrystallization from isopropyl acetate gave the lactams as white crystals. Fast-eluting compound (**20a**, axial): yield 590 mg (38%); mp 151.5−152 °C; ^{1}H-NMR (CDCl$_3$, δ) 1.0 (t, 3H, J = 7.3 Hz), 1.5−1.9 (m, 3H), 2.3−2.5 (m, 1H), 2.8−3.0 (m, 2H), 3.4−3.5 (m, 1H), 3.6−3.8 (m, 2H), 3.8 (s, 3H), 4.6 (d, 1H, J = 9.5 Hz), 5.6 (s, 1H), 6.8 (dd, 1H), 7.0 (d, 1H, J = 8.3 Hz), 7.1 (br s, 1H), 7.3−7.4 (m, 3H), 7.6 (d, 2H, J = 7.4 Hz); ^{13}C-NMR (CDCl$_3$, δ) 11.3, 21.3, 25.2, 26.7, 43.5, 55.2, 57.2, 71.3, 78.2, 109.5, 113.8, 126.0, 127.3, 127.9, 128.4, 129.1, 135.8, 137.2, 158.1, 167.5; IR (NaCl) 1651 cm^{-1} (CO); MS (M$^+$) 351.

Slow-eluting compound **20b** (equatorial): yield 840 mg (55%); mp 112.5−113.5 °C; ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 3H, J = 7.4 Hz), 1.4−1.6 (m, 1H), 1.6−1.9 (m, 2H), 2.4−2.5 (m, 1H), 2.9−3.0 (m, 2H), 3.1−3.3 (m, 1H), 3.8 (s, 3H), 3.8−4.0 (m, 2H), 4.80 (d, 1H, J = 9.3 Hz), 5.4 (s, 1H), 6.9 (m, 1H), 7.0−7.2 (m, 2H), 7.5−7.6 (m, 3H), 7.7−7.8 (m, 2H); ^{13}C-NMR (CDCl$_3$, δ) 11, 21, 25, 27, 43, 55, 57, 77, 81, 110, 115, 126, 127.9, 128, 130, 135.5, 138, 158, 169; IR (NaCl) 1640 cm^{-1} (CO); MS (M$^+$) 351. Anal. (C$_{22}$H$_{25}$NO$_3$) C, H, N. The equatorial product is used for the following step.

***trans*-9-Methoxy-2-phenyl-4-*N*-*n*-propyl-2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2*b*][1,4]oxazine (21).** To a solution of amide **20a** (350 mg, 1.0 mmol) in anhydrous THF (25 mL) was added LiAlH$_4$ (200 mg). The mixture was refluxed for 3 h, and then successively added were water (0.2 mL), 4 N NaOH (0.2 mL), and water (0.6 mL). This mixture was refluxed for another 15 min. The solid was filtered off, and the filtrate was dried over Na$_2$SO$_4$ and concentrated to yield 316 mg (94%) of

oil. The amine was converted to the HCl salt: mp 209−210 °C; ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 3H, J = 7.3 Hz), 1.5−1.7 (m, 3H), 2.3−2.4 (m, 4H), 2.8−2.9 (m, 3H), 3.1 (dd, 1H, J = 11.7 Hz), 3.8 (s, 3H), 4.6 (d, 1H, J = 9.03 Hz), 4.9 (dd, 1H, J = 10.5 Hz), 6.7−6.8 (m, 1H), 7.0 (d, 1H, J = 8.3 Hz), 7.2 (m, 1H), 7.3−7.5 (m, 5H); ^{13}C-NMR (CDCl$_3$, δ) 10.5, 17.0, 22.8, 25.8, 53.6, 53.9, 58.1, 60.3, 76.7, 77.5, 108.6, 112.2, 124.6, 125.6, 126.1, 126.8, 127.5, 136.0, 139.2, 156.36. Anal. (C$_{22}$H$_{27}$NO$_2$·HCl) C, H, N.

***trans*-9-Hydroxy-2-phenyl-4-*N*-*n*-propyl-2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2*b*][1,4]oxazine (2).** The phenol **2** was prepared from the methoxy compound **21** by essentially the same procedure as described for the preparation of **1b** from **17a**. The yield was 60%. An analytical sample was recrystallized from acetonitrile to provide white crystals: mp 202−204 °C; ^{1}H-NMR (CD$_3$OD, δ) 0.9 (t, 3H, J = 7.1 Hz), 1.6−1.9 (m, 3H), 2.3−2.4 (m, 1H), 2.7−2.9 (m, 2H), 3.0−3.2 (m, 1H), 3.3−3.5 (m, 3H), 4.2−4.3 (d, 1H, J = 12.9 Hz), 4.7 (d, 1H, J = 9.5 Hz), 5.5 (br s, 1H), 6.9 (d, 1H, J = 8.5 Hz), 6.6−6.7 (m, 1H), 7.1 (s, 1H), 7.3−7.6 (m, 5H); ^{13}C-NMR (CD$_3$OD, δ) 9.8, 15.1, 20.4, 25.0, 49.5, 52.6, 61.9, 68.9, 69.6, 110.6, 114.4, 123.7, 124.9, 127.0, 128.0, 128.2, 133.3, 135.8, 154.7. Anal. (C$_{21}$H$_{25}$NO$_2$·HCl·^{1}/$_2$H$_2$O) C, H, N.

***N*-*n*-Propyl-3-thiophen-2-yl-acetamide.** To a solution of *n*-propylamine (5.9 g, 100 mmol) in dichloromethane (50 mL) and 2 N NaOH (10 mL) was added dropwise 3-thienylacetyl chloride **22** (2.8 g, 17.4 mmol) dissolved in dichloromethane (10 mL). The reaction mixture was stirred for 2 h at room temperature. The two layers were separated, and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to yield 2.3 g (72%) of oil which solidified upon standing and was recrystallized from ethyl acetate/hexane: ^{1}H-NMR (CDCl$_3$, δ) 0.8 (t, 3H, J = 7.3 Hz), 1.4−1.5 (m, 2H), 3.16−3.22 (m, 2H), 3.6 (s, 2H), 5.6 (br s, 1H), 7.0−7.1 (m, 1H), 7.1−7.2 (m, 1H), 7.3−7.4 (m, 1H); ^{13}C-NMR (CDCl$_3$, δ) 9.7, 21.2, 36.6, 39.8, 122.2, 125.2, 127.0, 133.5, 169; IR (NaCl) 1641 cm^{-1} (C=O, amide). Anal. (C$_9$H$_{13}$NOS) C, H, N.

***N*-*n*-Propyl-(3-thiophen-2-yl-ethyl)-amine (23).** *N*-*n*-Propyl-3-thiophen-2-yl-acetamide (1.0 g, 5.5 mmol) was dissolved in anhydrous THF (25 mL), and 2 M BH$_3$·Me$_2$S (5.5 mL, 10.9 mmol) in anhydrous THF (20 mL) was slowly added at room temperature. The mixture was stirred at room temperature for 30 min and was subsequently refluxed for 1 h. The mixture was allowed to cool to room temperature; successively MeOH (3.5 mL), H$_2$O (3.5 mL), and 4 N HCl (3.5 mL) were added, and the mixture was stirred for another 30 min. The solvent was evaporated, and the residue was dissolved in H$_2$O and washed with diethyl ether; the aqueous layer was made alkaline with NaHCO$_3$ and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and filtered, and the solvent was evaporated to yield 0.75 g (67%) of yellow oil: ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 3H, J = 7.3 Hz), 1.5 (q, 2H, J = 7.3 Hz), 1.5−1.6 (m, 2H), 2.5 (t, 2H, J = 7.2 Hz), 2.8 (s, 4H), 6.9−7.0 (m, 2H), 7.2−7.3 (m, 1H); ^{13}C-NMR (CDCl$_3$, δ) 10.2, 21.6, 29.2, 48.7, 50.2, 119.4, 124.0, 126.6, 138.8. Anal. Calcd for C$_9$H$_{15}$NS·^{3}/$_4$H$_2$O: C, 59.14; H, 9.10; N, 7.66. Found: C, 59.60; H, 8.68; N, 7.30. The amine was converted to the HCl salt and recrystallized from diethyl ether/2-propanol: mp 207−210 °C.

***N*-*n*-Propyl-(3-thiophen-2-yl-ethyl)-thiophen-2-yl-ace-tamide (24).** To a solution of amine **23**·HCl (500 mg, 2.4 mmol) dissolved in dichloromethane (50 mL) and 10% NaOH (10 mL) was added 2-thienylacetyl chloride (2 mL). The mixture was stirred for 3 h at room temperature and poured into water. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The oil was purified over a SiO$_2$ column with dichloromethane as the eluent. Evaporation of the dichloromethane yielded 660 mg (93%) of oil: ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 3H, J = 7.3 Hz), 1.4−1.7 (m, 2H), 2.8−2.9 (m, 2H), 3.1−3.2 (m, 1H), 3.3−3.4 (m, 1H), 3.5−3.7 (m, 4H),

6.8−7.0 (m, 4H), 7.2−7.3 (m, 2H); ^{13}C-NMR (CDCl$_3$, δ) 9.7 (C10), 9.9 (C10), 19.3 (C9 or C12), 20.8 (C9 or C12), 26.7 (C9 or C12), 28.1 (C9 or C12), 33.3 (C6), 33.4 (C6), 46.0 (C8 or C11), 46.2 (C8 or C11), 47.6 (C8 or C11), 49.1 (C8 or C11), 119.8, 120.3, 123.2, 124.1, 124.5, 124.8, 125.2, 126.5, 126.7, 135.2, 136.5, 137.8, 168.2 (C7). Anal. (C$_{15}$H$_{19}$NOS$_2$) C, H, N.

N-n-Propyl-(2-thiophen-2-yl-ethyl)-thiophen-3-ylethyl-amine (3). *N-n*-Propyl-(3-thiophen-2-yl-ethyl)-thiophen-2-yl-acetamide **24** (0.5 g, 1.70 mmol) was dissolved in anhydrous THF (40 mL), and 2 M BH$_3$·Me$_2$S (3 mL) in anhydrous THF (10 mL) was slowly added at room temperature. The mixture was stirred at room temperature for 30 min and subsequently refluxed for 3 h. The mixture was allowed to cool to room temperature; successively MeOH (3 mL), H$_2$O (3 mL), and 12 N HCl (3 mL) were added, and the mixture was stirred for another 30 min. The solvent was evaporated, and the residue was dissolved in H$_2$O and washed with diethyl ether; the aqueous layer was made alkaline with the addition of NaHCO$_3$ and extracted with diethyl ether. In both diethyl ether layers, compound **3** was present, and therefore, all the organic layers were combined. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and filtered, and the solvent was evaporated to yield 0.33 g (69.3%) of a light yellow solid: mp 141.5−142.5 °C; ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 3H, J = 7.3 Hz), 1.5 (q, 2H, J = 7.3 Hz), 2.5−2.6 (m, 2H), 2.8−2.9 (m, 6H), 3.0−3.1 (m, 2H), 6.8 (m, 1H), 6.9−7.0 (m, 3H), 7.1−7.2 (m, 1H), 7.2−7.3 (m, 1H); ^{13}C-NMR (CDCl$_3$, δ) 10.5, 19.0, 26.4, 26.6, 53.5, 54.4, 54.5, 119.1, 121.8, 123.1, 123.7, 125.1, 126.9, 139.4, 141.7. Anal. (C$_{15}$H$_{21}$NS$_2$·ditoluoyl tartaric acid) C, H, N.

N-n-Propyl-(3-thiophen-2-yl-ethyl)-thiophen-3-yl-acet-amide (25). *N-n*-Propyl-(3-thiophen-2-yl-ethyl)-amine **23** (1.0 g, 6.0 mmol) was dissolved in dichloromethane (50 mL), and 10% NaOH solution (10 mL) and 3-thienyl acetyl chloride (1.0 g, 6.2 mmol) in dichloromethane (20 mL) were added. The reaction mixture was stirred for 2 h at room temperature. The two layers were separated, and the organic layer was washed with 3 N HCl solution and water and dried over Na$_2$SO$_4$, and the solvent was evaporated to yield 1.2 g (85.7%) of yellow oil: ^{1}H-NMR (CDCl$_3$, δ) 0.9 (dt, 3H, J = 7.3 Hz), 1.4−1.7 (m, 2H), 2.7−2.9 (m, 2H), 3.0−3.2 (m, 1H), 3.3−3.4 (m, 1H), 3.5−3.7 (m, 4H), 6.8−7.0 (m, 4H), 7.2−7.3 (m, 2H); ^{13}C-NMR (CDCl$_3$, δ) 9.7 (C10), 9.9 (C10), 19.3 (C9 or C12), 20.7 (C9 or C12), 26.7 (C9 or C12), 28.0 (C9 or C12), 34.3 (C6), 45.6 (C8 or C11), 46.0 (C8 or C11), 47.6 (C8 or C11), 48.9 (C8 or C11), 119.7, 120.2, 120.4, 120.5, 124.0, 124.3, 124.7, 126.5, 126.8, 127.2, 133.5 (C4 or C13), 133.6 (C4 or C13), 136.8 (C4 or C13), 137.8 (C4 or C13), 169.1 (C7); IR (NaCl) 1642 cm^{-1} (C=O, amide). Anal. (C$_{15}$H$_{19}$NOS$_2$·^{1}/$_2$H$_2$O) C, H, N.

N-n-Propyl-(3-thiophen-2-yl-ethyl)-thiophen-3-ylethyl-amine (4). This compound was synthesized in 67% yield according to the method used for compound **3**: mp 117−119 °C; ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 3H, J = 7.3 Hz), 1.5−1.8 (m, 2H), 2.8−3.0 (m, 4H), 3.0−3.2 (m, 4H), 6.9−7.1 (m, 4H), 7.2−7.3 (m, 2H); ^{13}C-NMR (CDCl$_3$, δ) 10.1, 14.8, 23.0, 53.0, 58.5, 119.9, 124.6, 126.5, 136.7. Anal. (C$_{15}$H$_{21}$NS$_2$·HCl·^{1}/$_4$H$_2$O) C, H, N.

3-(Dimethylaminomethyl)-2-(trimethylsilylmethyl)-thiophene (27). To a cooled solution of 2-bromo-3-(dimethylaminomethyl)thiophene (**26**) (47 g, 0.21 mol) and bis-(triphenylphosphine)nickel(II) chloride (1.4 g, 2.6 mol %) in anhydrous diethyl ether (500 mL) was added dropwise a solution of trimethylsilylmethylmagnesium chloride (prepared from magnesium (8.9 g, 0.37 mol), a crystal iodine, and chloromethyltrimethylsilane (40.9 g, 0.34 mol)) in anhydrous diethyl ether (20 mL). After being refluxed for 20 h, the mixture was cooled, andwater (160 mL) and aqueous saturated NH$_4$Cl solution (160 mL) were slowly added. The two layers were separated, and the aqueous layer was extracted with diethyl ether. The combined diethyl ether layers were washed with brine, dried over Na$_2$SO$_4$, and filtered, and the solvent was evaporated to yield 37 g (76%) of an oil: ^{1}H-NMR (CDCl$_3$, δ) 0.02 (s, 9H), 2.16 (s, 6H), 2.2 (s, 2H), 3.2 (s, 2H), 6.9 (s, 2H); ^{13}C-NMR (CDCl$_3$, δ) −1.7, 18.1, 45.0, 56.5, 119.3, 129.1, 132, 138 (ref 30).

3-(Trimethylammonium)-2-(trimethylsilylmethyl)thio-phene Iodide (28). To a stirred solution of 3-(dimethylami-nomethyl)-2-(trimethylsilylmethyl)thiophene (**27**) (3 g, 0.013 mol) in acetonitrie (10 mL) was added iodomethane (1.3 mL, 0.021 mol). After being refluxed for 1 h, the mixture was cooled to room temperature, and diethyl ether was added. The mixture was filtered to yield 3.45 g (71%) of a yellow solid compound: ^{1}H-NMR (DMSO, δ) 0.0 (s, 9H), 2.5 (s, 2H), 3.0 (s, 9H), 4.4 (s, 2H), 7.1 (d, J = 5.4 Hz, 1H), 7.3 (d, J = 5.4 Hz, 1H); ^{13}C-NMR (DMSO, δ) −1.4, 18.5, 51.7, 60.3, 122.3, 123.1, 130.8, 147.7 (ref 30).

5- and 6-Methylcarboxylate-4,5,6,7-tetrahydrobenzo-[*b*]thiophene (29a,b). To a stirred solution of 2-(trimethyl-silylmethyl)-3-(trimethylammonium)thiophene iodide (**28**) (10 g, 0.03 mol) and methylacrylate (136 mL) in acetonitrile (270 mL) was added dropwise a solution of tetrabutylammonium-fluoride trihydrate (17.1 g, 0.05 mol) in acetonitrile (540 mL) in 2 h. After the addition was complete, the solution was concentrated, and diethyl ether was added until no further precipitate was formed. The mixture was filtered, and the solvent was evaporated. Bulb-to-bulb distillation at 100 °C (0.05 mmHg) yielded 4.2 g (81%) of oil: ^{1}H-NMR (CDCl$_3$, δ) 1.8−2.0 (m, 1H), 2.15−2.3 (m, 1H), 2.6−3.1 (m, 5H), 3.7 (s, 3H), 6.7 (d, 1H, J = 5.1 Hz), 7.1 (d, 1H, J = 5.1 Hz); 5-isomer ^{13}C-NMR (CDCl$_3$, δ) 23.9, 26.1, 27.8, 39.6, 51.6, 122.3, 127.2, 133.3, 134.3, 175.3; 6-isomer ^{13}C-NMR (CDCl$_3$, δ) 24.4, 25.6, 27.1, 40.3, 51.6, 122.3, 127.1, 133.3, 134.3, 175.3; the ratio of 6-isomer/5-isomer = 2:1, which was determined by ^{13}C-NMR; IR (NaCl) 1739 cm^{-1} (C=O).

4,5,6,7-Tetrahydrobenzo[*b*]thiophene-5- and -6-Car-boxylic Acid (30a,b). A solution of 4,5,6,7-tetrahydrobenzo-[*b*]thiophene-5- and -6-carboxylate (**29a**,**b**) (4.29 g, 22 mmol) in an aqueous 16% NaOH solution (35 mL) was refluxed for 45 min. After the mixture had been cooled to rt, an aqueous 2 N HCl solution was added until the pH was 1. A white solid was formed which dissolved in dichloromethane. The aqueous layer was saturated with NaCl and extracted with dichloromethane. The combined organic layers were dried over Na$_2$-SO$_4$ and filtered, and the solvent was evaporated to yield 3.87 g (97%) of a pale yellow solid: mp 82.5−84.5 °C; ^{1}H-NMR (CDCl$_3$, δ) 1.8−2.1 (m, 1H), 2.2−2.3 (m, 1H), 2.7−3.1 (m, 5H), 6.8 (d, 1H, J = 5.1 Hz), 7.1 (d, 1H, J = 5.1 Hz); 5-isomer ^{13}C-NMR (CDCl$_3$, δ) 23.7, 25.8, 27.5, 39.5, 122.3, 127.2, 133.0, 134.3, 181.5; 6-isomer ^{13}C-NMR (CDCl$_3$, δ) 24.3, 25.3, 26.8, 40.1, 122.3, 127.1, 133.0, 134.3, 181.2. A 2:1 ratio of the 6-isomer:5-isomer was determined by ^{13}C-NMR.

5- and 6-Ammonium-4,5,6,7-tetrahydrobenzo[*b*]thio-phene Hydrochloride (31a,b). To a solution of a mixture of **30a** and **30b** (4.26 g, 23 mmol) and triethylamine (3.62 g, 24 mmol) in dioxane (120 mL) was added diphenylphosphoryl azide (5.3 mL, 24 mmol) at 5 °C. The reaction mixture was stirred overnight at room temperature. Diethyl ether (300 mL) and water (300 mL) were added to the reaction mixture. After separation of the two layers, the organic layer was washed with a 1% NaOH solution, dried over Na$_2$SO$_4$, and concen-trated under reduced pressure, yielding a red residue which was used without purification for the next step. To the residue were added aqueous 1 N HCl (110 mL) and dioxane (110 mL), and the mixture was heated for 2 h at 120 °C. The mixture was allowed to cool to room temperature, and it was basified (pH 10) with 4 N NaOH, extracted with diethyl ether, and dried over Na$_2$SO$_4$. Filtration and evaporation of the organic solvents gave a brown oil which dissolved in diethyl ether. Slow addition of an ethereal HCl solution gave a light brown solid. The yield of the obtained mixture of regioisomers (**31a,b**) was 2.6 g (58%): mp 192.8−194.1 °C; ^{1}H-NMR (CDCl$_3$, δ) 1.5−1.7 (m, 1H), 1.9−2.0 (m, 1H), 2.4−3.0 (m, 4H), 3.1−3.3 (m, 1H), 6.7 (d, 1H, J = 5.1 Hz), 7.0 (d, 1H, J = 5.1 Hz); 5-isomer ^{13}C-NMR (CDCl$_3$, δ) 21.9, 31.8, 34.0, 45.9, 121.0, 126.0, 132.1, 132.4; 6-isomer ^{13}C-NMR (CDCl$_3$, δ) 22.4, 31.1, 33.3, 46.4, 120.9, 125.7, 132.1, 132.9; IR (KBr) 3300 and 1618 cm^{-1} (NH$_2$). A 2:1 ratio of the 6-isomer:5-isomer was determined by ^{13}C-NMR.

5- and 6-(*N*-(Di-*n*-propyl))amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene (10 and 11). To a stirred solution of 5- and 6-ammonium-4,5,6,7-tetrahydrobenzo[*b*]thiophene chloride (**31a,b**) (2.5 g, 0.013 mol) and K$_2$CO$_3$ (7.05 g, 0.05 mol) in DMF (370 mL) was added 1-iodopropane (9 mL, 0.092 mmol). After being stirred for 24 h at 50 °C, the solution was poured into water and extracted 5 times with diethyl ether. The combined diethyl ether layers were washed 6 times with brine, dried over Na$_2$SO$_4$, filtered, and evaporated to yield 3 g (84%). It is possible to separate both isomers by column chromatography with the eluent EtOAc/hexane (1:9). After evaporation of the solvent, the isomers were dissolved in anhydrous diethyl ether, and 1 N HCl in diethyl ether was added to yield 1.3 g (36%) of the 6-isomer and 650 mg (18%) of the 5-isomer. 6-Isomer: mp 134−135 °C; ^{1}H-NMR (CDCl$_3$, δ) 1.0 (t, 6H, *J* = 7.3 Hz), 1.8 (q, 4H, *J* = 7.6 Hz), 2.0−2.2 (m, 1H), 2.3−2.4 (m, 1H), 2.7−3.0 (m, 2H), 3.0−3.4 (m, 6H), 3.7−3.9 (m, 1H), 6.8 (d, 1H, *J* = 5.1 Hz), 7.2 (d, 1H, *J* = 5.1 Hz); ^{13}C-NMR (CDCl$_3$, δ) 9.6, 18.0, 18.2, 23.5, 23.6, 24.7, 52.2, 52.7, 60.5, 123.4, 126.3. Anal. (C$_{14}$H$_{23}$NS·HCl) C, H, N. 5-Isomer: mp 134−136 °C; ^{1}H-NMR (CDCl$_3$, δ) 1.0 (t, 6H, *J* = 7.2 Hz), 1.8 (q, 6H, *J* = 7.3 Hz), 2.0−2.2 (m, 1H), 2.3−2.4 (m, 1H), 2.8−3.0 (m, 2H), 3.0−3.3 (m, 6H), 3.7−3.9 (m, 1H), 6.8 (d, 1H, *J* = 5.1 Hz), 7.2 (d, 1H, *J* = 5.1 Hz); ^{13}C-NMR (CDCl$_3$, δ) 9.6, 18.0, 18.3, 23.1, 24.1, 25.4, 52.2, 52.7, 60.2, 123.4, 126.7, 131, 133.5. Anal. (C$_{14}$H$_{23}$NS·HCl·^{1}/$_4$H$_2$O) C, H, N.

5- and 6-(*N*-(Di-*n*-propyl))methyleneamino-4,5,6,7-tetrahydrobenzo[*b*]thiophene (12, 13). To a cooled and stirred solution of 4,5,6,7-tetrahydrobenzo[*b*]thiophene-5- and -6-carboxylic acid (**30a,b**) (2.7 g, 0.015 mol) in anhydrous dichloromethane (40 mL) was added dropwise under nitrogen oxalyl chloride (5.9 mL, 8.9 g, 0.068 mol). The mixture was stirred overnight at room temperature and evaporated to yield 2.9 g (96%) of an oil of compound **33a,b**: ^{1}H-NMR (CDCl$_3$, δ) 1.9−2.2 (m, 1H), 2.3−2.5 (m, 1H), 2.7−3.3 (m, 5H), 6.8 (d, 1H, *J* = 5.0 Hz), 7.1 (d, 1H, *J* = 5.0 Hz); 5-isomer ^{13}C-NMR (CDCl$_3$, δ) 23.5, 26.3, 28.0, 51.6, 123.0, 127.0, 132.0, 134.3, 176.1; 6-isomer ^{13}C-NMR (CDCl$_3$, δ) 24.0, 25.8, 27.4, 52.0, 123.0, 127.0, 131.8, 134.1, 176.1. A 2:1 ratio of the 6-isomer:5-isomer was determined by ^{13}C-NMR. The reaction product was used for the next step without further purification and analysis.

To a stirred solution of 4,5,6,7-tetrahydrobenzo[*b*]thiophene-5- and -6-carbanoyl chloride (**32a,b**) (1.8 g, 8.8 mmol) in dichloromethane (100 mL) was added dropwise a mixture of di-*n*-propylamine (1.8 mL, 1.3 g, 0.013 mmol) and triethylamine (1.3 mL, 0.95 g, 0.010 mmol) in dichloromethane. After being stirred for 3 h at room temperature, the mixture was evaporated, and the residue was dissolved in diethyl ether. The diethyl ether layer was extracted 4 times with 4 N HCl, dried over Na$_2$SO$_4$, and evaporated. Purification with column chromatography (SiO$_2$) with the eluent EtOAc:hexane (1:9) yielded 1.66 g (71%) of an oil of compound **33a,b**: ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 6H, *J* = 7.4 Hz), 1.5−1.6 (m, 4H), 1.9−2.0 (m, 2H), 2.7−3.0 (m, 5H), 3.2−3.3 (m, 4H), 6.7 (d, 1H, *J* = 5.1 Hz), 7.0 (d, 1H, *J* = 5.1 Hz); 5-isomer ^{13}C-NMR (CDCl$_3$, δ) 10.9, 11.1, 20.7, 22.6, 24.4, 27.2, 28.8, 37.1, 47.4, 49.3, 122.1, 127.3, 134.1, 134.2, 174.6; 6-isomer ^{13}C-NMR (CDCl$_3$, δ) 10.9, 11.1, 20.7, 22.6, 24.9, 26.7, 28.1, 37.7, 47.4, 49.3, 122.0, 127.1, 134.1, 134.2, 174.6. A 2:1 ratio of the 6-isomer:5-isomer was determined by ^{13}C-NMR. The reaction product was used for the next step without further purification and analysis.

A solution of 4,5,6,7-tetrahydrobenzo[*b*]thiophene-5- and-6-carboxylic amide (**33a,b**) (5 g, 19 mmol) in anhydrous THF (340 mL) was cooled to 0−5 °C, and LiAlH$_4$ (3.6 g, 95 mmol) was added. The mixture was refluxed for 3 h; it was then cooled to room temperature, and 3.6 mL of water, 3.6 mL of 4 N NaOH solution, and 10.8 mL of water were added. The mixture was filtered; the precipitate was washed with diethyl ether, and the filtrate was dried over Na$_2$SO$_4$. Evaporation of the solvent yielded 4.5 g (92%) of crude oil. Purification and separation over a SiO$_2$ column with the eluent CH$_2$Cl$_2$/MeOH (20:1) yielded 3.7 g of 6-isomer and 1 g of 5-isomer: ^{1}H-NMR (CDCl$_3$, δ) 0.9 (t, 6H, *J* = 7.3 Hz), 1.4−1.5 (m, 6H), 1.9−2.1 (m, 2H), 2.3−2.5 (m, 6H), 2.7−3.0 (m, 3H), 6.8 (d, 1H, *J* = 5.1

Hz), 7.1 (d, 1H, *J* = 5.1 Hz); 5-isomer mp 118.5−120.5 °C; ^{13}C-NMR (CDCl$_3$, δ) 11.7, 20.2, 24.3, 28.3, 30.5, 32.9, 56.7, 60.2, 121.7, 127.5, 135.2, 135.3. Anal. (C$_{15}$H$_{25}$NS·^{1}/$_4$H$_2$O) C, H, N. 6-Isomer: mp 79−81 °C; ^{13}C-NMR (CDCl$_3$, δ) 11.7, 20.2, 24.8, 27.6, 29.8, 33.8, 56.7, 60.2, 121.6, 127.2, 135.2, 135.3. Anal. (C$_{15}$H$_{25}$NS·C$_4$H$_4$O$_4$) C, H, N.

6,7-Dihydro-5*H*-benzo[*b*]thiophen-4-one Oxime (35). 6,7-Dihydro-5*H*-benzo[*b*]thiophene-4-one (**34**) (10.0 g, 66.0 mmol) was dissolved in ethanol (120 mL) and water (12 mL). To this solution were added sodium acetate (11 g, 134 mmol) and hydroxylammoniumchloride (8.67 g, 125 mmol). This mixture was refluxed for 3 h, and then cooled to room temperature. Cold water was added, and the precipitate obtained was filtered, washed with water, and dried to yield 13.06 g (118%) that was not pure. Recrystallization of the white precipitate from ethanol gave white crystals: mp 125−127 °C; IR (KBr) 3289 cm^{-1} (C=N); ^{1}H-NMR (CDCl$_3$, δ) 2.0 (t, 2H, *J* = 6.3 Hz), 2.8−2.9 (m, 4H), 7.1 (d, 1H, *J* = 5.3 Hz), 7.3 (d, 1H, *J* = 5.4 Hz); ^{13}C-NMR (CDCl$_3$, δ) 22.2, 22.6, 24.8, 122.9, 123.1, 131, 143.7, 153.1. Anal. (C$_8$H$_9$NOS) C, H, N.

6,7-Dihydro-5*H*-benzo[*b*]thiophen-4-one *O*-Tosyloxime (36). A solution of oxime **35** (4.0 g, 23.9 mmol) in 25 mL of pyridine was cooled to about 10 °C in an ice bath. *p*-Toluene sulfonyl chloride (10.3 g, 53.9 mmol) was added slowly in small portions. This mixture was stirred for 2 h at about 10 °C, and then for 2 h at room temperature. The mixture was then poured into ice water. The precipitate obtained was filtered, washed with water, and dried. The yield was 7.84 g (100%) that was not pure. Recrystallization of the white precipitate from ethyl acetate gave white crystals: mp 130−132 °C; IR (KBr) 1596 cm^{-1} (C=N); ^{1}H-NMR (CDCl$_3$, δ) 1.9 (t, 2H, *J* = 6.2 Hz), 2.4 (s, 3H), 2.8−2.9 (m, 4H), 7.0 (d, 1H, *J* = 5.2 Hz), 7.2 (d, 1H, *J* = 5.3 Hz), 7.4 (d, 2H, *J* = 8.3 Hz), 7.9 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR (CDCl$_3$, δ) 21.8, 22.3, 23.8, 24.6, 123.2, 123.4, 128.8, 128.9, 129.5, 133, 145, 148, 159. Anal. (C$_{15}$H$_{15}$NO$_3$S$_2$·^{1}/$_2$H$_2$O) C, H, N.

5-Amino-6,7-dihydro-5*H*-benzo[*b*]thiophene-4-one (37). A solution of potassium *tert*-butoxide (5.7 g, 50.8 mmol), ethanol (43 mL), and toluene (107 mL) was cooled to 0−5 °C. To this solution was added 4-tosyloxime-4,5,6,7-tetrahydrothianaphthene (**36**) (10.0 g, 31.6 mmol). This mixture was stirred for 2 h at 0−5 °C, and then stirred for 2 h at room temperature. The precipitate (potassium tosylate) obtained was filtered and washed with diethyl ether. To the filtrate was added 5 mL of 37% HCl. After the mixture had been stirred for some time, a precipitate arose of the ketamine·HCl **37**. The precipitate was filtered and washed with diethyl ether, and the yield was 4.5 g (71%) before recrystallization; after recrystallization of the precipitate from ethanol/diethyl ether, yellow crystals were obtained: mp 197−199 °C; IR (KBr) 3430 (NH), 1600, 1500 (NH), 1676 cm^{-1} (C=O); ^{1}H-NMR (CD$_3$OD, δ) 2.3−2.5 (m, 1H), 2.6−2.7 (m, 1H), 3.3−3.4 (m, 2H), 4.3−4.4 (dd, 1H, *J* = 13.7 Hz), 7.4 (s, 2H); ^{13}C-NMR (CD$_3$OD, δ) 24.6, 30.2, 55.7, 124.9, 126.4, 135, 158, 188.

2-Chloro-*N*-(4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-5-yl)-acetamide (38). To a solution of amino ketone **37** (5.3 g, 21.1 mmol) in dichloromethane (290 mL) was added a solution of NaOH (7.1 g, 0.18 mol) in water (61 mL). To this stirred mixture was added chloroacetyl chloride (5.9 g, 4.2 mL, 51.9 mmol), and the mixture was stirred for another 3 h. After the reaction was complete, the organic layer was separated. To the water layer were added water (145 mL) and 4 N HCl until the water layer was neutral. The water layer was extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and evaporated. Recrystallization from ethyl acetate/hexane yielded 6.0 g (95%) of brown crystals: mp 130−132 °C; IR (KBr) 3334 (NH), 1681 (C=O), 1639 cm^{-1} (C=O, amide); ^{1}H-NMR (CDCl$_3$, δ) 1.9−2.1 (m, 1H), 2.8−2.9 (m, 1H), 3.15−3.25 (m, 1H), 4.1 (s, 2H), 4.5−4.65 (m, 1H), 7.1 (d, 1H, *J* = 5.3 Hz), 7.3 (d, 1H, *J* = 5.4 Hz), 7.6 (m, 1H); ^{13}C-NMR (CD$_3$OD, δ) 24.6, 31.3, 42.6, 55.9, 124.5, 124.7, 135.6, 155.7, 166.4, 189. Anal. (C$_{10}$H$_{10}$NO$_2$SCl) C, H, N.

***trans*-2-Chloro-*N*-(4-hydroxy-4,5,6,7-tetrahydrobenzo-[*b*]thiophene-5-yl)-acetamide (39).** A solution of chloroacetamide (**38**) (4.0 g, 16.4 mmol) in methanol (90 mL) under nitrogen was cooled to 5–8 °C in an ice bath. While the mixture was being stirred, a solution of NaBH$_4$ (1.5 g, 39.6 mmol) was added in portions. The solution was stirred for another hour at 5–8 °C. To the mixture was added 1 N HCl to remove excess of NaBH$_4$, and then the solvent was evaporated. Recrystallization of the crude product from ethyl acetate/hexane yielded 3.55 g (88%) of brown crystals: mp 148–150 °C; IR (KBr) ~3200 (OH), 1646 cm^{-1} (C=O, amide); ^{1}H-NMR (CDCl$_3$, δ) 1.85–2.05 (m, 1.5H), 2.15–2.3 (m, 1.5H), 2.8–3.0 (m, 2H), 4.1 (s, 2H), 4.2 (m, 1H), 4.6 (d, 1H, *J* = 7.17 Hz), 6.7 (br s, 1H), 7.1 (d, 1H, *J* = 5.0 Hz), 7.2 (d, 1H, *J* = 5.1 Hz); ^{13}C-NMR 23.3, 27.6, 42.9, 54.1, 69.8, 124.1, 127.4, 127.5, 128, 169. Anal. (C$_{10}$H$_{12}$NO$_2$SCl) C, H, N.

***trans*-4,5a,6,9a-Tetrahydro-5*H*-9-oxa-6-aza-cyclopenta-[*a*]naphthalene-7-one (40).** To a solution of 4-hydroxyamide (**39**) (5.2 g, 21.16 mmol) in 2-propanol (275 mL) was added dropwise 50% NaOH solution (3.6 mL) at room temperature. The solution was stirred for 15 h. After the reaction was complete, the solvent was evaporated until almost dry. The suspension was diluted with water (180 mL), neutralized with 10% HCl, and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and evaporated. Recrystallization of the crude product from ethyl acetate/hexane yielded 2.0 g (45%) of brown crystals: mp 242–244 °C; IR (KBr) 3313 (NH), 1638 cm^{-1} (C=O); ^{1}H-NMR (CDCl$_3$, δ) 1.9–2.1 (m, 1H), 2.1–2.2 (m, 1H), 2.9–3.0 (m, 2H), 3.6–3.7 (m, 1H), 4.4 (d, 2H, *J* = 2.7 Hz), 4.47–4.53 (m, 1H), 7.0 (d, 1H, *J* = 5.2 Hz), 7.2 (d, 1H, *J* = 5.2 Hz), 7.9 (br s, 1H); ^{13}C-NMR 23.5, 27.6, 53.8, 68.3, 76.1, 124.2, 124.5, 133.9, 136.3, 170.2. Anal. (C$_{10}$H$_{11}$NO$_2$S) C, H, N.

***trans*-2,3,4a,5,6,9b-Hexahydro-4*H*-thianaphth[4,5*e*][1,4]-oxazine (14).** A solution of *trans*-2,3,4a,5,6,9b-hexahydro-4*H*-thianaphth[4,5*e*][1,4]oxazine-3-one (**40**) (1.3 g, 6.2 mmol) in anhydrous THF (195 mL) was cooled to about 5 °C. To this solution was added LiAlH$_4$ (845 mg, 22.3 mmol). This mixture was refluxed for 2 h, and then cooled to room temperature. Water (0.9 mL), 4 N NaOH solution (0.9 mL), and water (2.7 mL) were successively added to remove excess LiAlH$_4$. The mixture was filtered and washed with diethyl ether, and the filtrate was dried over Na$_2$SO$_4$. Evaporation under reduced pressure of the solvent yielded an oil.The oil was dissolved in anhydrous diethyl ether which was saturated with gaseous HCl. Recrystallization from 2-propanol anhydrous diethyl ether yielded 245 mg (17%) of white crystals: mp 264–266 °C; IR (KBr) 3213 cm^{-1} (NH); ^{1}H-NMR (CDCl$_3$, δ) 1.2–1.3 (m, 1H), 2.1–2.3 (m, 1H), 2.4–2.6 (m, 1H), 2.9–3.1 (m, 2H), 3.2–3.3 (m, 1H), 3.3–3.5 (m, 2H), 3.7–3.8 (m, 1H), 3.9–4.0 (m, 1H), 4.8–4.9 (m, 1H), 7.0 (d, 1H, *J* = 5.4 Hz), 7.3 (d, 1H, *J* = 5.4 Hz); ^{13}C-NMR (CDCl$_3$, δ) 23.9, 26.1, 45.2, 58.0, 64.8, 76.3, 125.1, 125.5, 134.5, 136.5. Anal. (C$_{10}$H$_{13}$NOS·HCl·^{1}/$_4$H$_2$O) C, H, N.

***trans*-*N*-*n*-Propyl-2,3,4a,5,6,9b-hexahydro-4*H*-thianaphth[4,5*e*][1,4]oxazine (15).** To a solution of *trans*-2,3,-4a,5,6,9b-hexahydro-4*H*-thianaphth[4,5*e*][1,4]oxazine (**14**) (100 mg, 0.43 mmol) in DMF (12 mL) under nitrogen were added anhydrous K$_2$CO$_3$ (230 mg, 1.7 mmol) and 1-iodopropane (490 mg, 290 μL, 2.9 mmol). This mixture was stirred at 55 °C for 2.5 h. From TLC (with 10:1 CH$_2$Cl$_2$/MeOH as the eluent), it was clear that the reaction was not finished, so additional 1-iodopropane was added, and the mixture was allowed to stand over the weekend at room temperature. The mixture was poured into water (20 mL) and extracted with diethyl ether (5 × 20 mL). The combined extracts were washed with brine (6 × 20 mL), dried over Na$_2$SO$_4$, and evaporated. The resulting oil was dissolved in anhydrous diethyl ether, and diethyl ether saturated with gaseous HCl was added to prepare the HCl salt in a yield of 94.35 mg (80%): mp 238–240 °C; ^{1}H-NMR (CDCl$_3$, δ) 1.1 (t, 3H, *J* = 7.3 Hz), 1.7–2.1 (m, 3H), 2.6–2.8 (m, 1H), 3.0–3.2 (m, 3H), 3.3–3.7 (m, 4H), 4.1–4.2 (m, 2H), 4.8 (d, 1H, *J* = 9.1 Hz), 7.0 (d, 1H, *J* = 5.1 Hz), 7.2 (d,

1H, 5.2 Hz); ^{13}C-NMR (CDCl$_3$, δ) 10.9, 17.6, 23.4, 24.1, 52.6, 55.4, 65.0, 65.6, 76.7, 125.3, 125.5, 135, 147. Anal. (C$_{13}$H$_{19}$-NOS·HCl) C, H, N.

Distance Calculating. Conformational analyses were performed in MacroModel version 6.5 on a Silicon Graphics O$_2$ workstation.[33] All ligands were considered in their protonated, positively charged forms (MM3* force field[34]), and were minimized using the Truncated Newton Conjugate Gradient (TNCG) minimizer in a simulated distance-dependent GB/SA water continuum.[35] After the minimization, the distances were calculated.

Pharmacology. Cell Lines Expressing Dopamine (DA) Receptor Isoforms. A cell line expressing the human DA D$_{2L}$ was purchased from Dr. O. Civelli (Oregon Health Sciences University). The D$_{2L}$ receptor cDNA was subcloned into the expression vector, pRc/CMV. The plasmids were transfected by electroporation into CHO K1 cells. A single stable transfectant, resistant to the antibiotic G418, was isolated and selected for use in the binding studies. The human DA D$_3$ receptor cDNA cloned in the pcDNAIneo plasmid was obtained from Dr. K. O'Malley and stably transfected into CHO K1 cells by a modified calcium phosphate precipitation technique.[36] Transfectants were selected in G418, isolated, and screened for the expression of human D$_3$ receptors by radioligand binding as previously described.[37]

Cell Culture and Preparation of Cell Membranes. CHO K1 cells expressing either human DA D$_{2L}$ or D$_3$ receptors were grown in 162 cm^2 culture flasks in F12 medium (Gibco Laboratories, Grand Island, NY) supplemented with 10% fetal bovine serum (FBS, Hyclone, Logan, UT) in an atmosphere of 5% CO$_2$/95% air at 37 °C. Cells were grown until confluent, after which growth medium was removed and replaced with 0.02% EDTA in a phosphate-buffered saline solution (Sigma Chemical Co., St. Louis, MO), and the cells were scraped from the flasks. The cells were centrifuged at about 1000*g* for 10 min at 4 °C; they were then resuspended in TEM buffer (25 mM Tris-HCl, pH 7.4 at 37 °C, 1 mM EDTA, and 6 mM CaCl$_2$) for D$_{2L}$ and D$_3$ and homogenized with a Brinkman Polytron homogenizer at setting 5 for 10 s. The membranes were pelleted by centrifugation at 20000*g* at 4 °C for 20 min, and then the pellets were resuspended in the appropriate buffer at 1 mL/flask and stored at −70 °C until they were used in the receptor binding assay.

Receptor Binding Assays: D$_{2L}$ and D$_3$ DA Receptors. A cell membrane preparation (400 μL) was incubated in triplicate with 50 μL of [^{3}H]N-0437 (2 nM for D$_{2L}$) or [^{3}H]-spiperone (0.5 nM for D$_3$), 50 μL of buffer, or competing drugs where appropriate to give a final volume of 0.5 mL. After 60 min of incubation at 25 °C, the incubations were terminated by the rapid filtration through Whatmann GF/B glass fiber filters (soaked for 1 h in 0.5% polyethylenimine) on a Brandel MB-48R cell harvester and by 3 washes with 1 mL of ice-cold buffer. Individual filter disks containing the bound ligand were placed in counting vials with 4 mL of scintillation fluid (Ready Gel, Beckman Instrument Inc., Fullerton, CA), and then counted in a Beckman LS-6800 liquid scintillation counter at an efficiency of 45%. Nonspecific binding was defined in the presence of 1 μM haloperidol.

Data Calculation. Saturation and competition binding data were analyzed using the iterative nonlinear least-squares curve-fitting Ligand program. In competition experiments, apparent K_i values were calculated from IC$_{50}$ values by the method of Cheng and Prusoff.[38] Experimental compounds were made up as stock solutions in dimethyl sulfoxide (DMSO). The final concentration of 0.1% DMSO used in the incubation mixture had no effect on the specific binding. Each observation was carried out in triplicate. To allow for these calculations, K_d values were measured for the interaction of various ligands with the receptor. The interactions measured were for the following: [^{3}H]spiperone binding, human D$_3$, 0.15 ± 0.02 nM (*n* = 3); and [^{3}H]N-0437 binding, human D$_{2L}$, 2.24 ± 0.05 nM (*n* = 3).

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