Substituted Hexahydrobenzo[*f*]thieno[*c*]quinolines as Dopamine D1-Selective Agonists: Synthesis and Biological Evaluation *in Vitro* and *in Vivo*

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A series of substituted 9,10-dihydroxyhexahydrobenzo[*f*]thieno[*c*]quinolines (TB[f]Q), varying with respect to the position of the thiophene relative to the benzo[*f*]quinoline core and the nature and position of the substituent on the thiophene, were prepared and evaluated for their affinity and selectivity for the dopamine D1-like receptor. The thieno[3,2-*c*]B[*f*]Q regioisomers bearing a small alkyl (C1−C3) substituent at the 2 position were potent (K_i < 20 nM) and selective (D2/D1 > 50) D1 agonists with close to full agonist activity (IA > 85%). The compounds were resolved and found to exhibit a high level of enantiospecificity in their interaction with the D1 receptor. Selected compounds were tested *in vivo* in the 6-OHDA rodent model of Parkinson's disease and for their liability to produce seizure-like activities in mice. (5a*R*)-*trans*-2-Propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol (**5**) emerged as the compound with the best overall *in vivo* profile in terms of potency (ED_{50} = 0.04 μmol/kg) and safety.

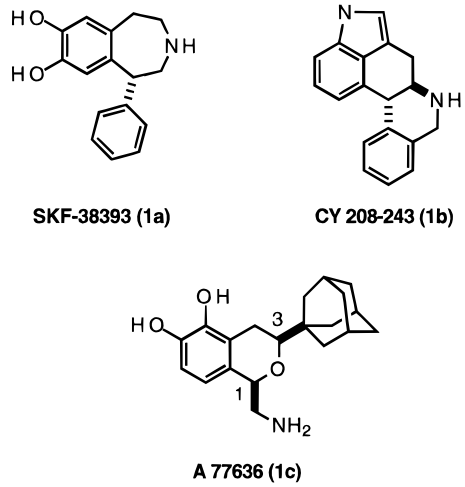
Introduction

Dopamine receptors can be divided into either the D1-like or the D2-like family of subtypes based on their pharmacological profiles and coupling with the enzyme adenylate cyclase.[1] Molecular cloning techniques have shown that the D1-like family is further divided into the D1 and D5 receptors, both of which activate adenylate cyclase, and the D2-like family is divided into the D2, D3, and D4 receptors, which either inhibit cyclic adenosine monophosphate (cAMP) production or are not coupled to adenylate cyclase.[2]

Parkinson's disease (PD) is characterized by the degeneration of dopamine-secreting neurons in the nigrostriatal pathway.[3] Dopamine agonist replacement therapy with L-Dopa, which is endogenously converted to dopamine and thereby stimulates both the D1 and the D2 families of receptors, remains the cornerstone of PD therapy.[4] Long-term treatment with L-Dopa, however, is associated with the induction of drug-related side effects such as dyskinesia and on−off phenomena (motor fluctuations). Direct-acting D2-selective agonists such as bromocriptine, lisuride, and pergolide are also prescribed, although their use is primarily as add-on therapy to L-Dopa since they demonstrate limited efficacy as monotherapy.[5]

The therapeutic benefit of D1-selective agonists in treating PD has not yet been fully explored. Initial results with the prototypical D1 agonist SKF-38393 (**1a**) showed lack of efficacy in both an MPTP-lesioned primate model of PD and clinical trials.[6] The lack of efficacy of SKF-38393 has been attributed to its low intrinsic activity *in vitro* (ca. 10−40% relative to DA) in both primate and human caudate tissues and to its questionable levels of brain penetration.[7] The benzergoline CY208-243 (**1b**), another D1-selective partial agonist, was efficacious in MPTP-lesioned primates and produced a weak, albeit significant, improvement in PD patients.[8]

Chart 1. Dopamine D1-Selective Agonists



The recent identification of novel structural classes of D1-selective full DA agonists has led to renewed interest in the potential utility of D1 agonists for the treatment of PD. Isochromans, typified by A-77636 (**1c**), are potent and selective full agonists at the D1-receptor.[9] Isochroman **1c** was shown to be effective in both primate and rodent models of PD;[9b] however, its development was precluded because of the rapid behavioral desensitization observed after repeated administration.[10]

Dihydrexidine (**2**), a benzophenanthridine that functions as a D1 full agonist, was also shown to be effective in a primate model of PD and is reported to be in clinical development.[11] We have investigated the structurally related series of substituted hexahydrothieno[*c*]benzo[*f*]quinolines **3** (TB[f]Q), in which the phenyl ring in dihydrexidine is replaced with its thiophene bioisostere. It is noteworthy that these compounds were originally

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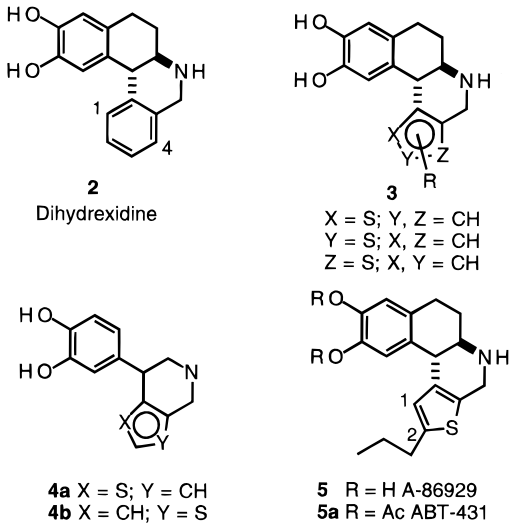
Chart 2



designed as conformationally restricted analogs of the fully efficacious D1 agonists **4a**,**b**.[12]

We have previously reported compound **5** (A-86929: (5a*R*,11b*S*)-4,5,5a,6,7,11b-hexahydro-2-propyl-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol) to be a potent and selective full agonist at the D1 receptor that is efficacious in rodent and primate models of PD after both acute and long-term (30 days) administration.[13] The diacetyl prodrug (**5a**) of **5** imparts greater long-term solid-state stability, is readily converted to the parent compound (**5**) under physiological conditions, and is currently under clinical development. We now wish to report on the synthesis of substituted regioisomeric hexahydrothieno[*c*]benzo[*f*]quinolines **3** and the results of subsequent structure−activity studies that led to the selection of **5** as a clinical candidate.

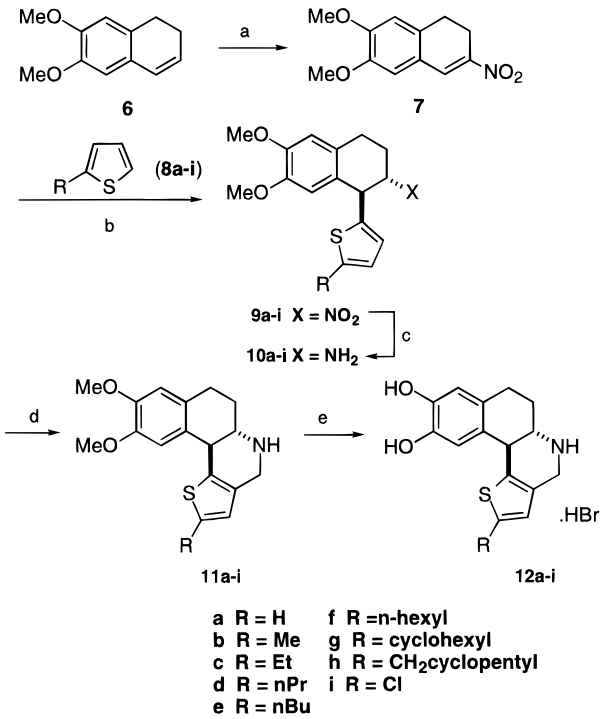
Chemistry

Synthetic schemes 1−8 were used to prepare the compounds described in this report. The compounds vary with respect to the positioning of the thiophene ring relative to the benzo[*f*]quinoline nucleus and the type and site of substitution on the thiophene. The compounds were first prepared in racemic form, in a convergent manner through the addition of an appropriately substituted thiophene to either the nitroolefin **7** (Schemes 1−6) or the nitroolefin **41** (Scheme 7). Selected compounds were then resolved into their respective enantiomers using chiral HPLC (Scheme 8).

The hexahydrothieno[3,2-*c*]benzo[*f*]quinolines **12a**−**i** were prepared by lithiation and subsequent Michael addition of a 2-substituted thiophene (**8**) to the nitroolefin **7** (Scheme 1). Compound **7** was synthesized from the dihydronaphthalene **6** via nitration with tetranitromethane in pyridine.[14] The thiophenes employed were either commercially available or prepared via one of the following literature methods: (i) alkylation of 2-lithiothiophene with either alkyl halides or trialkylboranes[15] or (ii) Friedel−Crafts acylation followed by Wolff−Kishner deoxygenation.[16] Lithiation of **8** with *n*-BuLi and subsequent Michael addition to the nitroolefin **7** gave adduct **9** as a ca. 3:1 *cis*:*trans* mixture of diastereomers. Equilibration of this crude mixture under thermodynamic conditions, with triethylamine, typically afforded a 4−5:1 mixture of diastereomers in favor of the *trans* product **9**. Chromatographic separation followed by reduction of the *trans* product to the amine **10** with zinc in acetic acid proceeded in high yield with retention of stereochemistry. The tetracycle **11** was then constructed via a modified Pictet−Spengler cyclization.[17] Thus, the amine **10** was reacted first with paraformaldehyde in methanol in the presence of K_2CO_3 to form an intermediate *N*,*O*-acetal or imine, which was then treated with TFA in CH_2Cl_2 to effect cyclization in 25−40% yield. Standard Pictet−Spengler conditions (formalin, HCl) gave very poor yields (<5%) of **11**. Deprotection of the methyl ethers with BBr_3 gave the catecholamines **12a**−**i** in high yields.

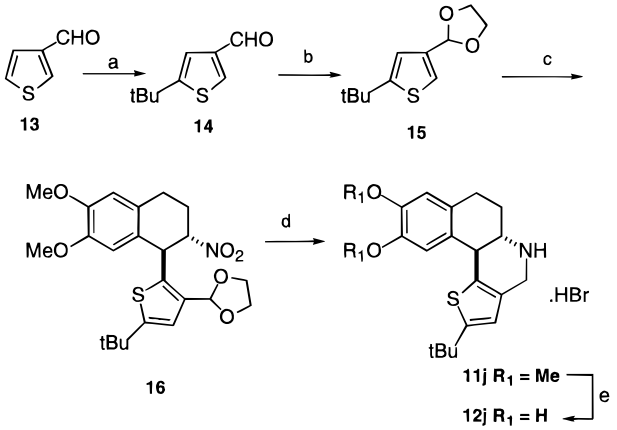
An alternative preparation of the thieno[3,2-*c*]B[*f*]Q series is outlined in Scheme 2. This method was applied to the synthesis of the *tert*-butyl derivative **12j**. Thus, Friedel−Crafts alkylation (*t*-BuBr, $AlCl_3$) of 3-thiophene carboxaldehyde followed by protection of the aldehyde produced the acetal **15**. Lithiation of **15** with *n*-BuLi followed by addition to the nitroolefin **7**, equilibration

Scheme 1[a]



[a] Reagents: (a) $C(NO_2)_4$, pyridine; (b) (1) *n*-BuLi, **8**, THF, (2) Et_3N, CH_3CN; (c) Zn, 6 M HCl; (d) (1) HCHO, K_2CO_3, (2) TFA; (e) BBr_3, CH_2Cl_2.

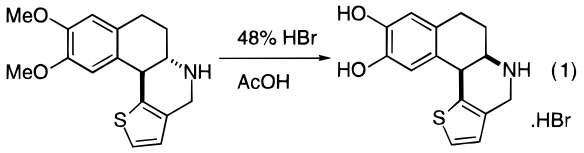
Scheme 2[a]



[a] Reagents: (a) *t*-BuBr, $AlCl_3$; (b) $HOCH_2CH_2OH$, TsOH; (c) (1) *n*-BuLi, **7**, (2) Et_3N; (d) Zn, HCl; (e) BBr_3, CH_2Cl_2.

of the resulting diastereomeric mixture, and chromatographic separation gave the *trans* nitro compound **16** in low yield (14%). The low yield can be partly attributed to competing lithiation at the acetal carbon. Lithiation of **15** with 1 equiv of *n*-BuLi followed by a D_2O quench gave a 1:1 mixture of compounds resulting from deuterium incorporation at either C2 or the acetal carbon, indicating a competitive rate of lithiation at C2 versus the acetal methine. Treatment of **16** with Zn in aqueous HCl afforded directly the tetracycle **11j** in moderate yield (20−30%). Apparently deprotection of the acetal led to an intermediate amino aldehyde that condensed to the imine, which was then reduced to give **11j**. BBr_3-mediated deprotection of the methyl ethers gave **12j**.

The isomeric *cis* thieno[3,2-*c*]B[*f*]Q **17** was obtained in quantitative yield via treatment of **11a** with refluxing HBr in AcOH (eq 1). The reaction presumably proceeds



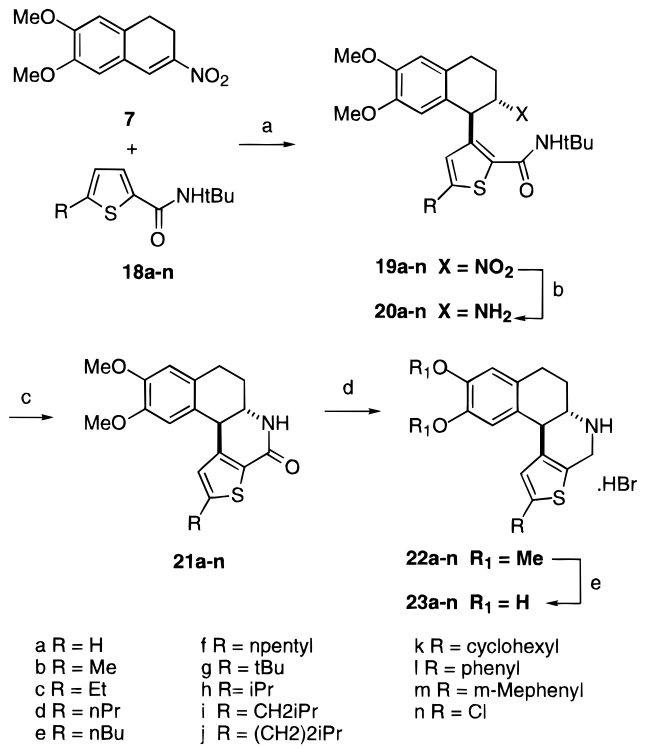
11a **17**

via the *trans* catechol **12a**, which undergoes epimerization to the *cis* compound under the reaction conditions. We had initially observed that BBr_3 deprotection of **11a** was accompanied by epimerization leading to varying amounts of the *cis* isomer depending on the reaction time. Deprotection of **11a** at 0 °C for only 10 min produced exclusively the *trans* isomer **12a**, whereas longer reaction times (3−4 h) led to mixtures containing >75% of the *cis* isomer **17**, suggesting epimerization of **12a** to **17**. It is interesting to note that no epimerization was observed when compounds bearing a substituent at the 2 position (**11b**−**i**) were deprotected under similar conditions (BBr_3, 0 °C, 2−3 h).

The synthesis of the 2-substituted thieno[3,2-*c*]B[*f*]Q analogs **23a**−**n** is outlined in Scheme 3. Lithiation of thiophene **18** and subsequent Michael addition to the nitroolefin **7** followed by Et_3N-mediated equilibration yielded the nitro adduct **19** with a *trans*:*cis* isomer ratio of greater than 15:1. The carboxamide group of **18** serves to both direct lithiation at the 3 position and to participate in the formation of the tetracycle. Thus, the nitro compound **19** was reduced to the amino amide **20**, which, after treatment of **20** with TsOH in refluxing toluene, afforded the lactam **21**.[18] Borane reduction and subsequent deprotection afforded the catechols **23a**−**n**.

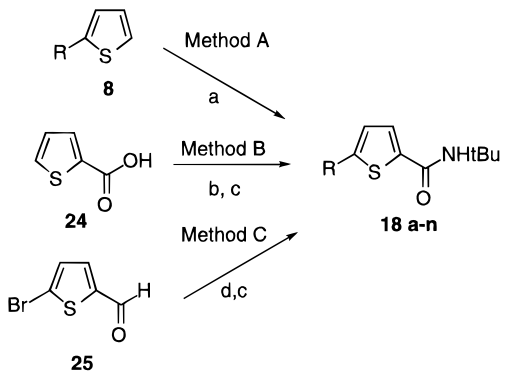
The requisite 5-substituted 2-thiophene carboxamides **18a**−**n** used in Scheme 3 were prepared using one of three methods (Scheme 4). In method A, 2-substituted thiophene **8** was lithiated with *n*-BuLi and then reacted with *tert*-butyl isocyanate to directly afford **18**. In method B (used for **18g**,**h**), thiophene-2-carboxylic acid (**24**) underwent Friedel−Crafts alkylation to give a 5-alkylthiophene-2-carboxylic acid. The resulting acid was converted to the acid chloride, which was then reacted with *tert*-butyl amine to give **18**. Method C was applied to the aryl-substituted compounds **18l**,**m** and involved palladium-catalyzed coupling of arylboronic acids with 2-bromo-5-thiophenecarboxaldehyde (**25**).[19] The 2-aryl-5-thiophenecarboxaldehyde obtained was

Scheme 3[a]



[a] Reagents: (a) (1) *n*-BuLi, THF, (2) Et_3N; (b) Zn, HCl; (c) TsOH, toluene, reflux; (d) BH_3·THF; (e) BBr_3.

Scheme 4[a]



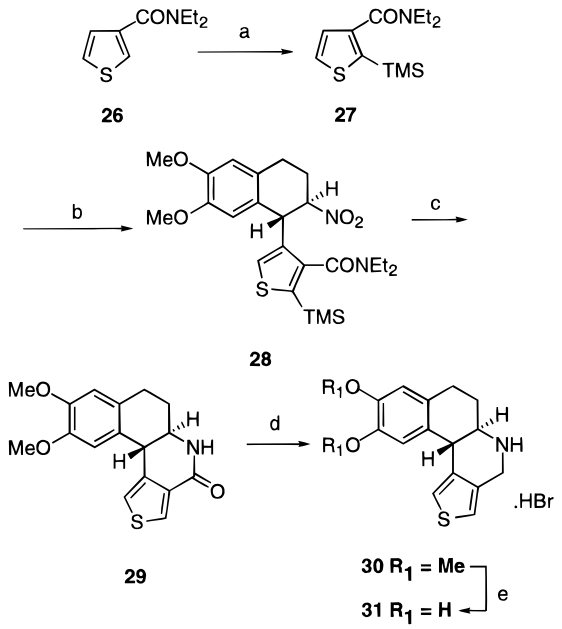
[a] Reagents: (a) (1) *n*-BuLi, (2) *t*-BuNCO; (b) RCl, $AlCl_3$; (c) (1) $SOCl_2$, (2) *t*-$BuNH_2$; (d) (1) $ArB(OH)_2$, $Pd(PPh_3)_4$, (2) $AgNO_3$, KOH.

oxidized to the acid and then converted to the corresponding *tert*-butylamide **18**, as in method B.

The synthesis of the 2-thia regioisomer **31** is shown in Scheme 5. The requisite 4-lithio-3-carboxamide thiophene was obtained by initially blocking the C2 position of commercially available **26** with a trimethylsilyl group. Exclusive 4-lithiation of the TMS-thiophene **27** and its subsequent addition to the olefin **7** and equilibration gave the *trans* adduct **28**. Reduction of the nitro group followed by removal of the TMS group gave the corresponding aminoamide, which underwent Me_3Al-mediated cyclization to afford the lactam **29**. The lactam was then reduced with borane to give **30**. BBr_3-mediated deprotection of the methyl ethers was accompanied by epimerization to give the catechol **31** as a 3:1 *trans*:*cis* mixture.

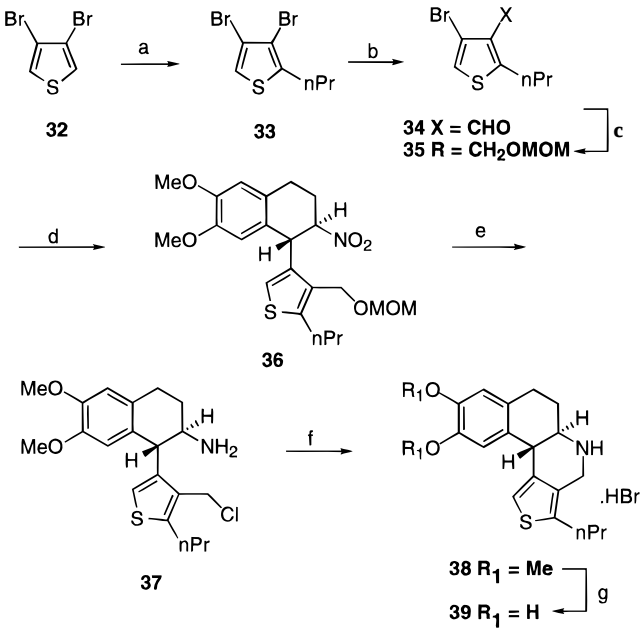
The synthesis of the 2-thia-3-alkyl regioisomer **39** is depicted in Scheme 6. Lithiation of 3,4-dibromothiophene (**32**) with LDA followed by reaction with *n*-propyl iodide gave **33**. Halogen−metal exchange and subsequent reaction with DMF afforded a 1:1 mixture of regioiso-

Scheme 5[a]



[a] Reagents: (a) *s*-BuLi, TMEDA, TMSCl; (b) (1) *s*-BuLi, TMEDA, **7**, (2) Et_3N; (c) (1) Zn, 6 M HCl, (2) Me_3Al, toluene, reflux; (d) BH_3·THF; (e) BBr_3.

Scheme 6[a]



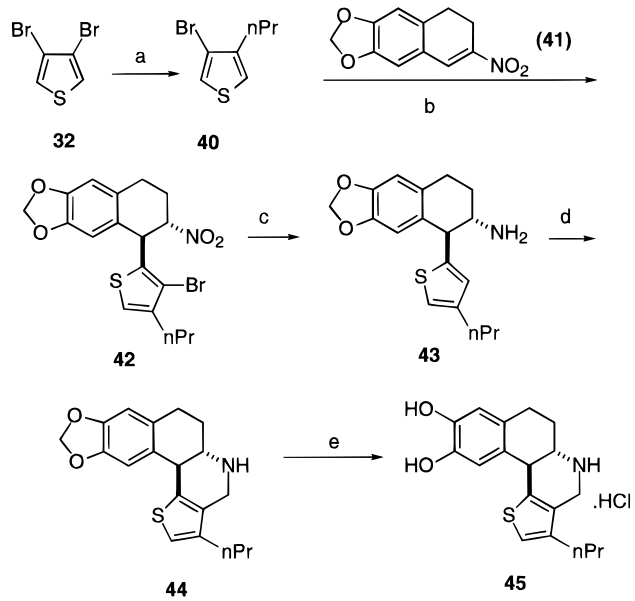
[a] Reagents: (a) LDA, *n*-PrI; (b) *n*-BuLi, DMF; (c) (1) $NaBH_4$, (2) MOM-Cl; (d) (1) *n*-BuLi, **7**, (2) Et_3N; (e) (1) Zn, HCl, (2) HCl, THF, H_2O; (f) K_2CO_3, *t*-BuOH; (g) BBr_3.

meric aldehydes. The desired aldehyde **34** was chromatographically separated and reduced to the alcohol that was protected as a MOM ether (**35**). Halogen−metal exchange followed by Michael addition to the nitroolefin **7** gave the adduct **36** in 57% yield. Reduction of the nitro group and treatment with aqueous HCl gave the amino chloride **37**, which underwent base-mediated cyclization to afford the tetracycle **38** (62% overall yield). Deprotection under the usual conditions with BBr_3 (0 °C, 2 h) was accompanied by significant epimerization to yield a ca. 1:1 mixture of *cis*:*trans* isomers. The *trans* isomer **39** was purified from the *cis* isomer using reverse-phase HPLC.

In view of the epimerization encountered in the deprotection of **38**, we used an alternative catechol protecting group that could be cleaved under milder conditions for the preparation of the 3-propylthieno[3,2-*c*]B[*f*]Q derivative **45** (Scheme 7). Halogen−metal exchange of **32** followed by acylation and Wolff−Kishner deoxygenation gave thiophene **40**. Lithiation of **40** with LDA occurred regiospecifically to give the corresponding 2-lithiothiophene which was allowed to react with the methylenedioxy-protected nitroolefin **41** to yield the adduct **42**. Reduction and dehalogenation of **42** followed by Pictet−Spengler cyclization gave **44**. Deprotection with BCl_3 gave **45**, as a 5:1 mixture of *trans*:*cis* isomers.

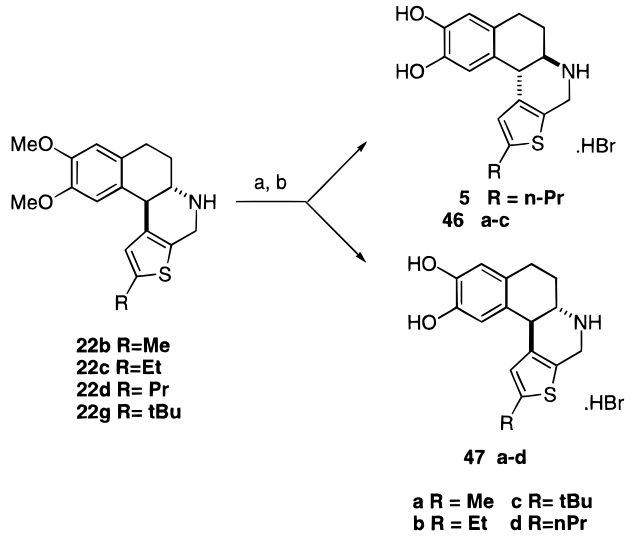
Racemic mixtures of selected compounds were resolved into their respective enantiomers using chiral HPLC (Scheme 8). Thus, the racemic amines **22b**−**d**,**g** were separated on a preparative Chiracel OD column to obtain the enantiomers in >98% ee as determined by analytical HPLC.[20] Deprotection of the methyl ethers gave the corresponding catechols **5**, **46a**−**c**, and **47a**−**d** in >98% ee.

Scheme 7[a]



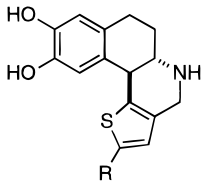
[a] Reagents: (a) (1) *n*-BuLi, $CH_3CH_2CON(MeO)Me$, (2) KOH, NH_2NH_2; (b) (1) LDA, **41**, (2) Et_3N; (c) (1) Zn, HCl, (2) H_2, Pd/C; (d) (1) $(HCHO)_n$, K_2CO_3, (2) TFA; (e) BCl_3.

Scheme 8[a]



[a] Reagents: (a) chiral HPLC separation; (b) BBr_3.

Table 1. *In Vitro* Pharmacology: SAR of 2-Alkylthieno[3,2-*c*]benzo[*f*]quinolines[a]



		binding affinity, K_i[b]			binding selectivity		functional activity, D1	
compd	R	D1-like (nM)	D2-like (nM)	α2 (nM)	D2/D1	α2/D1	EC_{50} (nM)	IA[c] (%)
12a	H	70 ± 15 (8)	340 ± 10 (8)	84 ± 15 (3)	5	1	39 ± 5.8 (3)	120 ± 3 (3)
12b	Me	18 ± 8.1 (3)	205 ± 15 (3)	100 ± 15 (3)	11	5	47 ± 11 (3)	85 ± 12 (3)
12c	Et	8.5 ± 2.4 (3)	145 ± 25 (3)	255 ± 67 (3)	17	26	50 ± 18 (3)	100 ± 12 (3)
12d	*n*-Pr	13 ± 3 (4)	150 ± 52 (3)	400 ± 110 (3)	11	30	28 ± 9.5 (3)	93 ± 2 (3)
12e	*n*-Bu	22 ± 3.9 (4)	450 ± 130 (3)	980 ± 78 (3)	20	44	44 ± 25 (3)	79 ± 4 (3)
12f	*n*-hexyl	690 ± 350 (3)	540 ± 115 (3)	>10000 (2)	1	>10	140 ± 35 (3)	76 ± 9 (3)
12g	cyclohexyl	165 ± 26 (4)	1530 ± 14 (3)	8900 ± 200 (5)	9	54	79 ± 28 (4)	87 ± 15 (4)
12h	CH_2cycloC5	280 ± 115 (4)	560 ± 72 (4)	7200 ± 1050 (2)	2	25	125 ± 70 (3)	63 ± 5 (3)
12i	Cl	4.3 ± 0.6 (3)	145 ± 58 (3)	595 ± 140 (2)	33	140	43 ± 5.9 (3)	97 ± 4 (3)
12j	*tert*-butyl	78 ± 19 (5)	910 ± 205 (6)	2450 ± 800 (3)	12	31	28 ± 5.1 (3)	74 ± 10 (3)
17	H (*cis*)	3800 ± 250 (5)	2800 ± 460 (4)	nd	1	nd	3200 ± 630 (4)	48 ± 2 (4)
				Reference Compounds				
1a	SKF-38393	35 ± 8.6 (23)	2900 ± 510 (21)	3050 ± 680 (3)	83	85	950 ± 400 (11)	58 ± 3 (11)
1c	A-77636	30 ± 5.4 (68)	1800 ± 135 (69)	1300 ± 240 (17)	60	43	8.2 ± 1.1 (29)	102 ± 4 (29)
2	DHX	100 ± 34 (17)	1400 ± 450 (18)	3000 ± 450 (8)	14	30	88 ± 20 (8)	130 ± 7 (8)

[a] Values represent the mean ± SEM, with the number of experiments in parentheses. [b] Binding ligands were as follows: D1, [^{125}I]SCH 23982; D2, [^{3}H]spiperone; α2, [^{3}H]rauwalsine. The tissues used were as follows: D1, D2, rat caudate membrane; α2, rat cortical membrane. [c] IA = intrinsic activity relative to dopamine.

Pharmacology

***In Vitro* Pharmacology.** The binding affinities (K_i) were determined in dopamine D1 and D2 receptor assays as well as in the adrenergic α2 receptor assay. It is important to note that the affinity determined for the D1 receptor in this series of experiments indicates affinity for the D1 family of receptors (D1 and D5), while the affinity determined for the D2 receptor indicates affinity for the D2 family of receptors (D2, D3, and D4). Rat caudate membrane was used as the tissue source for the D1 and D2 receptors, while rat cortical membrane was used as the source for the α2 receptor. [^{125}I]-SCH 23982, [^{3}H]spiperone, and [^{3}H]rauwalsine were used as the radioligands for the D1, D2, and α2 assays, respectively. The ability of a compound to stimulate the D1 receptor was assayed by measuring cAMP production in cell-free homogenates of goldfish retinal tissue. An EC_{50} value and intrinsic activity (IA, the magnitude of the response expressed as a percent relative to dopamine) were determined from this assay.

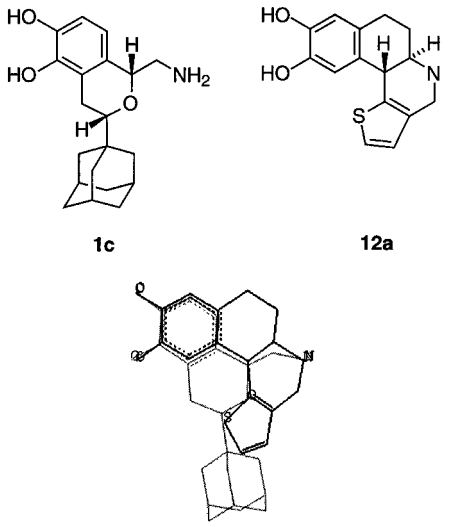
***In Vivo* Pharmacology.** Selected compounds were tested in the rat rotation model of PD.[21] This model is produced by discrete unilateral 6-hydroxydopamine injections into the brain that destroy a certain set of ascending dopamine-secreting neurons. As a result of the loss of dopaminergic input, DA receptors on the lesioned side become supersensitive, and administration of direct-acting DA agonists causes the animal to rotate away from (contralateral to) the lesioned side. The ED_{50} value (dose of a test compound at which one-half of the animals in the test group exhibit at least 50 net contralateral rotations in a 30-min period) and duration of action at the ED_{50} were determined.

Selected compounds were also tested for their ability to induce seizures in mice. Drug-induced seizures were scored by placing animals in cages, allowing them to habituate for 1 h, and then injecting them with drug. The animals were observed for the presence of behavioral seizure-like activity consisting of forelimb clonus with or without arching of the back and loss of balance. The ED_{50} is defined as the dose at which one-half of the test group animals displayed any of these behaviors during the observation period.

Results and Discussion

The compounds examined in this study can be divided into three structural classes depending on the positioning of the thiophene ring relative to the benzo[*f*]-quinoline nucleus and the site of the substituent on the thiophene ring: (a) 2-substituted 1-thia, (b) 2-substituted 3-thia, and (c) 3-substituted 1- or 2-thia. The *in vitro* pharmacological data for the 2-substituted 1-thia derivatives are presented in Table 1. The unsubstituted parent compound **12a** showed high affinity (K_i = 70 nM) and potent, full agonist activity (EC_{50} = 39 nM, IA = 120%) at the D1-like receptor. However, it suffers from

Chart 3. Superimposition of **1c** and **12a** (Bold)



poor selectivity (5-fold) over the D2-like receptor. As dopaminergic compounds are known to bind to other biogenic amine receptors, **12a** was screened for its binding affinity to adrenergic and serotonergic receptors. The compound had weak affinity (K_i > 5000 nM) for the adrenergic α1, 5HT1a, 5HT1c, and 5HT2 receptors but had significant affinity for the adrenergic α2 receptor (K_i = 84 nM) that was comparable to that for the D1 receptor. Therefore, we routinely screened all compounds for adrenergic α2 activity.[22]

Extensive evaluation of the structure−activity relationship inherent in the previously described isochroman series as well as modeling of the D1 and D2 receptors revealed that the D1 receptor differs from the D2 receptor in that the former posseses a putative lipophilic binding pocket that can accommodate a range of sterically demanding substituents.[23] The binding pocket can be accessed by substituting appropriate groups at the 3 position of the isochromans, e.g, the adamantyl group in isochroman **1c**. Interaction with this pocket by a compound is expected to confer selectivity and potency for the D1 receptor. Superimposing the structures of **1c** with **12a** suggested that the auxiliary lipophilic binding pocket is only partially filled by the thiophene ring of **12a** (Chart 3). Thus, we subsequently examined whether substituents on the thiophene ring could increase favorable interactions with the lipophilic binding pocket and thereby lead to increased selectivity and potency for the D1 receptor. Introduction of short (C1−C4) unbranched alkyl groups at the 2 position (**12b**−**e**) resulted in a consistent 3−8-fold increased affinity for the D1 receptor, whereas the effect on D2 receptor binding was variable and less pronounced. A decrease in affinity for the adrenergic α2 receptor was also observed. The 2-chloro compound **12i** showed both enhanced potency and selectivity for the D1 receptor. Compounds **12a**−**e**,**j** potently stimulated adenylate cyclase (EC_{50} = 28−50 nM) and possessed high intrinsic activity relative to dopamine. Although substitution with the bulky *tert*-butyl group (**12j**) was tolerated, introduction of extended alkyl groups (e.g., *n*-hexyl, cyclohexyl) (**12f**−**h**) resulted in decreased affinity for both dopaminergic and α2 receptors relative to the parent compound **12a**.

As previously noted with other benzo[*f*]quinolines such as the benzergoline **1b** and dihydrexidine (**2**), the *trans* ring juncture is essential for dopaminergic activity. Nichols has reported that the *cis* isomer of dihydrexidine binds very weakly at the D1 receptor (binding IC_{50} > 5 μM).[24] Consistent with these previous reports, the *cis* isomer **17** is much weaker than the *trans* isomer **12a** in both its binding affinity (50-fold) and functional activity (80-fold) at the D1 receptor.

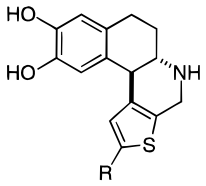
The data for the 2-substituted 3-thia series are shown in Table 2. The unsubstituted parent compound **23a** had high affinity (K_i = 73 nM) and functional potency for the D1-like receptor with good selectivity (18-fold) over the D2-like receptor but poor selectivity (2-fold) over the α2 receptor. A comparison of **23a** and **12a** reveals that changing the relative position of the thiophene sulfur atom from the 1 to the 3 position resulted in a 3−4-fold weaker affinity for the D2 receptor, whereas D1 receptor affinity was unaffected. In order to boost potency and selectivity for the D1 receptor in this particular series, we investigated the effect of substitution at the C2 position in an attempt to replicate the success previously observed upon substitution in the 1-thia series.

Introduction of substituents at the C2 position resulted in pronounced effects on D1 and α2 binding, whereas the effects on D2 were more moderate. Affinity for the α2 receptor decreased with increasing steric size of the C2 substituents. As observed with the 1-thia series, substitution with small alkyl groups (**23b**−**d**,**h**, Me, Et, *n*-propyl, isopropyl) led to increased affinity for the D1 receptor (K_i < 20 nM) and a concomitant decrease in affinity for the D2 and α2 receptors resulting in high levels of selectivity (D2/D1 K_is > 50). These compounds were potent D1 agonists (EC_{50} = 29−87 nM) stimulating adenylate cyclase with high intrinsic activity (IA = 82−99%). Introduction of a *tert*-butyl group (**23g**) resulted in maintenance of high D1 affinity and further decrease in D2 and α2 affinity. However, introduction of extended groups such as *n*-pentyl or isopentyl (**23f**,**j**) and phenyl (**23l**) resulted in a significant loss (4−15-fold) in D1 binding affinity. Further substitution of the pendant phenyl with a methyl group (**23m**) led to a dramatic decrease (>100-fold) in binding affinity.

The addition of substituents on the thiophene did not have a pronounced effect on the ability of the compound to stimulate adenylate cyclase. In general, there is good agreement between binding and cyclase values (see Table 2). However, as we have previously reported with the isochroman class of compounds, certain compounds (e.g., **23l**,**n**) can show a significant discrepancy between binding and cyclase values.[23] The reasons for this discrepancy remain unclear, although it could be partly attributed to the fact that different tissues from different species were used in the binding and functional assays. Additionally, these assays are only simple biochemical models of the complex signal transduction processes.

Compounds **12a**, **23a**, and dihydrexidine have comparable affinities for the D1-like receptor, whereas **12a** and **23a** have significantly higher affinity for the adrenergic receptor. However, as discussed above, introduction of small alkyl groups at the 2 position of either the 1-thia or the 3-thia series led to increased potency and selectivity for the D1 receptor. The same observation was reported on dihydrexidine upon substitution of small alkyl groups at either the 2 or the 3 position.[25] The results from the present thieno[*c*]benzo-

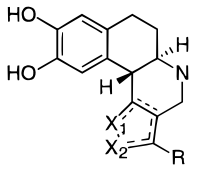
Table 2. *In Vitro* Pharmacology: SAR of 2-Alkylthieno[2,3-*c*]benzo[*f*]quinolines[a]



		binding affinity, K_i[b]			binding selectivity		functional assay, D1	
compd	R	D1-like (nM)	D2-like (nM)	α2 (nM)	D2/D1	α2/D1	EC_{50} (nM)	IA[c] (%)
23a	H	73 ± 25 (7)	1290 ± 330 (7)	185 ± 65 (3)	17	2	47 ± 3.9 (3)	98 ± 15 (3)
23b	Me	18 ± 3.4 (7)	980 ± 290 (7)	730 ± 205 (9)	54	40	87 ± 20 (7)	82 ± 4 (7)
23c	Et	6.5 ± 1.0 (3)	640 ± 96 (3)	940 ± 58 (3)	98	145	31 ± 7.8 (3)	95 ± 12 (3)
23d	*n*-Pr	18 ± 4.5 (5)	1400 ± 475 (3)	2220 ± 185 (3)	78	123	52 ± 18 (3)	99 ± 14 (3)
23e	*n*-Bu	125 ± 17 (6)	1320 ± 560 (6)	3800 ± 1360 (2)	10	30	77 ± 26 (3)	78 ± 3 (3)
23f	*n*-pentyl	520 ± 140 (3)	2090 ± 140 (3)	>10000 (2)	4	>19	170 ± 22 (3)	80 ± 11 (3)
23g	*tert*-butyl	51 ± 11 (5)	3260 ± 1030 (4)	7060 ± 1650 (5)	64	138	69 ± 15 (4)	97 ± 5 (4)
23h	*i*-Pr	20 ± 5.2 (4)	1720 ± 280 (4)	3000 ± 650 (3)	86	150	29 ± 4.3 (3)	87 ± 15 (3)
23i	CH_2-*i*-Pr	52 ± 8.6 (3)	2560 ± 490 (5)	7940 ± 2300 (3)	49	152	88 ± 11 (3)	84 ± 5 (3)
23j	CH_2CH_2-*i*-Pr	440 ± 100 (3)	1760 ± 530 (3)	>10000 (2)	4	>20	470 ± 270 (3)	67 ± 5 (3)
23k	cyclohexyl	150 ± 24 (3)	3110 ± 260 (3)	>20000 (2)	20	>130	94 ± 47 (3)	71 ± 7 (3)
23l	phenyl	1130 ± 220 (7)	2590 ± 650 (4)	6420 ± 890 (3)	2	5	80 ± 16 (7)	88 ± 11 (7)
23m	*m*-Me-phenyl	>7500 (6)	>10000 (6)	>20000 (2)			640 ± 430 (4)	70 ± 18 (4)
23n	Cl	12 ± 2.4 (9)	300 ± 98 (7)	2795 (1)	25	232	170 ± 60 (4)	91 ± 9 (4)

[a] Values represent the mean ± SEM, with the number of experiments in parentheses. [b] Binding ligands were as follows: D1, [^{125}I]SCH 23982; D2, [^{3}H]spiperone; α2, [^{3}H]rauwalsine. The tissues used were as follows: D1, D2, rat caudate membrane; α2, rat cortical membrane. [c] IA = intrinsic activity relative to dopamine.

Table 3. *In Vitro* Pharmacology: SAR of 3-Alkylthienobenzo[*f*]quinolines[a]



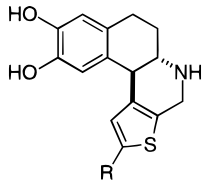
				binding affinity, K_i[b]			binding selectivity		functional activity, D1	
compd	X_1	X_2	R	D1-like (nM)	D2-like (nM)	α2 (nM)	D2/D1	α2/D1	EC_{50} (nM)	IA[c] (%)
31[d]	CH	S	H	45 ± 8 (3)	1030 ± 375 (4)	575 ± 140 (3)	22	12	240 ± 80 (4)	77 ± 7 (4)
39	CH	S	*n*-Pr	125 ± 92 (6)	100 ± 11 (6)	515 ± 58 (3)	1	4	82 ± 33 (4)	71 ± 3 (4)
45[e]	S	CH	*n*-Pr	58 ± 19 (3)	51 ± 13 (3)	nd[f]	1	nd	160 ± 58 (3)	98 ± 12 (3)

[a] Values represent the mean ± SEM, with the number of experiments in parentheses. [b] Binding ligands were as follows: D1, [^{125}I]SCH 23982; D2, [^{3}H]spiperone; α2, [^{3}H]rauwalsine. The tissues used were as follows: D1, D2, rat caudate membrane; α2, rat cortical membrane. [c] IA = intrinsic activity relative to dopamine. [d] Compound tested as a 3:1 *trans*:*cis* mixture of diastereomers. [e] Compound tested as a 5:1 *trans*:*cis* mixture. [f] Not determined.

[*f*]quinolines along with those from the dihydrexidine derivatives and the 3-substituted isochromans should provide additional insights in mapping the length and breadth of the putative lipophilic binding pocket of the D1 receptor.

The *in vitro* biological data for the 3-substituted compounds are shown in Table 3. The 2-thia compound **31** bound to the D1 receptor with comparable affinity as the regioisomeric **12a** and **23a**, although the former exhibited weaker potency in the functional assay. Introduction of a *n*-propyl group at the 3 position (**39**) resulted in a 2-fold decrease in D1 affinity and a 10-fold increase in D2 affinity relative to the parent **31**, providing a nonselective dopaminergic compound. Similarly, introduction of a *n*-propyl substituent at the 3 position of **12a** (compound **45**) resulted in a nonselective compound (D2/D1 K_i = 1). The increased affinity for the D2 receptor relative to D1 upon substitution at the 3 position of the thieno[*c*]benzo[*f*]quinolines was similar

Table 4. *In Vitro Pharmacology*: SAR of Homochiral 2-Alkylthieno[3,2-*c*]benzo[*f*]quinolines[a]



		binding affinity, K_i[b]			binding selectivity		functional activity, D1	
compd	R	D1-like (nM)	D2-like (nM)	α2 (nM)	D2/D1	α2/D1	EC_{50} (nM)	IA[c] (%)
5	(−)-*n*-Pr	14 ± 1.7 (30)	800 ± 190 (36)	4020 ± 850 (8)	57	290	24 ± 2.6 (19)	85 ± 3 (19)
47d	(+)-*n*-Pr	640 ± 130 (4)	5400 ± 1060 (3)	1410 ± 29 (2)	8	2	2700 ± 800 (3)	28 ± 5 (3)
46a	(−)-Me	5.7 ± 0.9 (4)	240 ± 70 (4)	870 ± 400 (3)	42	150	33 ± 6.8 (3)	87 ± 12 (3)
47a	(+)-Me	1520 ± 130 (3)	4790 ± 1670 (3)	2370 ± 1100 (2)	3	1	>10000 (3)	0% (3)
46b	(−)-Et	2.3 ± 0.3 (6)	345 ± 58 (5)	970 ± 360 (5)	150	420	22 ± 5.3 (4)	104 ± 4 (4)
47b	(+)-Et	790 ± 190 (6)	5450 ± 790 (6)	1360 ± 500 (3)	7	1.7	>10000 (3)	0% (3)
46c	(−)-*t*-Bu	6.6 ± 0.8 (7)	1380 ± 140 (9)	6410 ± 1050 (6)	210	970	24 ± 4.2 (9)	90 ± 11 (9)
47c	(+)-*t*-Bu	810 ± 150 (3)	4490 ± 260 (3)	>10000 (2)	5	>10	1750 ± 50 (3)	25 ± 3 (3)

[a] Values represent the mean ± SEM, with the number of experiments in parentheses. [b] Binding ligands were as follows: D1, [^{125}I]SCH 23982; D2, [^{3}H]spiperone; α2, [^{3}H]rauwalsine. The tissues used were as follows: D1, D2, rat caudate membrane; α2, rat cortical membrane. [c] IA = intrinsic activity relative to dopamine.

to that observed upon substitution at the C4 position of dihydrexidine.[25]

An analysis of the above *in vitro* data in Tables 1−3 revealed that the C2-alkyl (C1−C3)-substituted thieno-[3,2-*c*] series represented the most promising compounds in terms of potency and selectivity for the D1 receptor. Since these compounds were initially tested as racemic mixtures, we obtained the enantiomerically pure isomers for **23b**−**d**,**g**. The data shown in Table 4 reflect the high degree of enantioselectivity displayed by the D1 receptor for these compounds; the (+) enantiomers **47a**−**d** are 45−350-fold weaker in both binding and functional activity than the respective (−) enantiomers.[26] All the (−) enantiomers (**5**, **46a**−**c**) studied had similar *in vitro* profiles, exhibiting high affinity (K_i < 14 nM) and selectivity (D2/D1 > 50) for the D1 receptor while potently stimulating adenylate cyclase with high intrinsic activity (ranging from 85% to 104%) relative to dopamine.

The 6-OHDA rodent model of PD has been extensively used to characterize the central actions of dopaminergic compounds. DA agonists that are used clinically for the treatment of PD, including L-Dopa and D2-selective agonists, produce robust contralateral rotation in this model. Selected compounds from the thieno[3,2-*c*] series were tested in this model (Table 5). The enantiomerically pure compounds **5** and **46a**−**c** were potent in eliciting robust contralateral rotation after subcutaneous administration with ED_{50} values ranging from 0.04 to 0.05 μmol/kg. The racemic unsubstituted compound **23a** was also quite potent (0.06 μmol/kg). The *n*-butyl and isobutyl compounds (**23e**,**i**), despite their comparable *in vitro* profile relative to the parent (**23a**), were significantly weaker (0.5 and 2 μmol/kg, respectively) than **23a** in producing contralateral rotation in the lesioned rats.

Dopamine D1-selective agonists including A-77636 have been reported to produce a seizure-like response in nonlesioned rats and mice at high doses.[27] Selected compounds were tested for their ability to induce seizure-like activity in mice (Table 5). All the compounds tested induced seizure activity once a threshold dose was achieved. A comparison of the enantiomerically pure compounds **5** and **46a**−**c** shows that **5** has the greatest separation (>150-fold) between the doses required to elicit rotation (ED_{50} = 0.04 μmol/kg) versus those that produced seizure-like activity (ED_{50} = 7.55 μmol/kg). Compound **5** was further evaluated for its seizuregenic liability in rats. The doses required to induce seizures were substantially higher in rats than in mice (ED_{50} = 34.2 (rats) versus 7.5 (mice) μmol/kg, sc).

Table 5. *In Vivo* Pharmacology

compd	ED_{50}, rotation (sc, μmol/kg)[a]	duration at the ED_{50}	ED_{50}, seizures (sc, μmol/kg)[b]	ED_{50}(seizures)/ ED_{50}(rotation)
(±)-**23a**	0.06 (0.03−0.13)	0.5	15.5 (9.9−24.1)	260
(±)-**23e**	0.55 (0.31−0.95)	1.5	88.6 (57.8−135.8)	160
(±)-**23i**	2.0 (0.6−7.1)	1	nd[c]	
(−)-**5**	0.04 (0.02−0.1)	1.5	7.55 (6.3−9.4)	190
(−)-**46a**	0.05 (0.04−0.05)	1−1.5	1.02 (0.6−1.6)	20
(−)-**46b**	0.04 (0.01−0.1)	2	1.25 (0.8−1.9)	30
(−)-**46c**	0.04 (0.025−0.06)	2.5	3.4 (2.4−4.7)	85

[a] Dose at which one-half of the test group animals (rats) exhibit at least 50 net contralateral rotations in a 30 min period; 95% confidence limits shown in parentheses. [b] Dose at which one-half of the test group animals (mice) display seizure-like behaviors. [c] Not determined.

Conclusion

As part of a program at Abbott to develop potent and selective dopamine D1-like full agonists as a potential treatment for PD, a series of substituted thienobenzo-

[*f*]quinolines were prepared and tested for affinity to dopaminergic receptors, affinity to the adrenergic α2 receptor, and functional activity at the D1-like receptor. The position of the thiophene relative to the benzo[*f*]-quinoline core and the nature and position of the substituent on the thiophene were found to be important in optimizing the affinity and selectivity of these compounds for the D1 receptor. Introduction of small alkyl groups (C1−C4) at the 2 position of the 3-thia series was found to be optimal for potency and selectivity for the D1 receptor. This optimization was likely due to the ability of these compounds to better accommodate the putative lipophilic binding pocket that exists in the D1 receptor. The compounds also exhibited a high level of enantiospecificity in their interaction with the D1 receptor as the (+) enantiomers were 45−300-fold weaker in both binding and functional activity.

The compounds with the most promising *in vitro* profile were tested in the 6-OHDA rodent model of PD. Those compounds that were the most potent in eliciting contralateral rotation were further tested for their liability to produce seizure-like activities in mice. From this series of evaluations compound **5** emerged as the compound with the best overall *in vivo* profile in terms of potency and safety.

Compound **5** has been further characterized *in vitro* in human cloned dopamine receptors and *in vivo* in both rodent and primate models of PD and was found to be efficacious after both acute and long-term (30 days) administration.[13b] The diacetyl prodrug derivative of **5**, ABT-431 (**5a**), is currently in early clinical trials as a potential treatment for Parkinson's disease.

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. All spectral and analytical data were obtained through the Abbott analytical Department. All reactions were conducted in oven-dried or flame-dried glassware under a nitrogen atmosphere. Anhydrous solvents were purchased from Aldrich Chemical Co. Analytical thin-layer chromatography was performed by using 2.5 cm × 10 cm plates coated with a 0.25 mm thickness of silica gel containing PF 254 indicator (Analtech). Flash chromatography was performed using silica gel 60 (E. Merck 9285, 230−400 mesh). Elemental microanalysis gave results for the elements stated within ±0.4% of the theoretical values.

1,2-Dihydro-6,7-dimethoxynaphthalene (6). To a cloudy solution of 6,7-dimethoxy-1-tetralone (60 g, 0.29 mol) in 600 mL of ethanol was added $NaBH_4$ (13.2 g, 0.35 mol) in portions over 0.5 h, and the mixture was stirred for 14 h at room temperature. Most of the solvent was removed by evaporation, and to the residue was added 100 mL of water. The resulting suspension was heated to 45 °C for 45 min, cooled to room temperature, and then extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to leave an oily residue. The crude intermediate alcohol was dissolved in 600 mL of toluene heated to reflux and then treated with 0.55 g (2.9 mmol) of *p*-toluenesulfonic acid (added carefully so as to avoid boiling over), and the solution was heated at reflux for 30 min. The reaction mixture was cooled to room temperature, poured into water, basified with aqueous $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated to afford 55 g (99% yield) of **6**: ^{1}H NMR ($CDCl_3$) δ 6.67 (s, 1H), 6.60 (s, 1H), 6.38 (d, 1H, J = 10 Hz), 5.94 (dt, 1H, J = 4, 10 Hz), 3.88 (s, 3H), 3.86 (s, 3H), 2.73 (t, 2H, J = 8 Hz), 2.32−2.24 (m, 2H).

1,2-Dihydro-6,7-dimethoxy-3-nitronaphthalene (7). Tetranitromethane (34 g, 0.17 mol) was added slowly (streamwise addition over 5−10 min) to a 0 °C solution of **6** (30 g, 0.16 mol) and pyridine (15 mL, 0.19 mol) in 200 mL of acetone, and the reaction mixture was stirred for 5 min. The reaction was then quenched with 200 mL of 1 M aqueous KOH, and the mixture was stirred at 0 °C for 20 min resulting in a thick yellow precipitate. The precipitate was filtered off, washed with water, and dried in a vacuum oven overnight to afford 27.5 g (74%) of **7** as a yellow solid: mp 90.5−1.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (s, 1H), 6.82 (s, 1H), 6.75 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 2.98 (m, 4H).

Caution: Tetranitromethane has been reported to be explosive in the presence of impurities; thus all the appropriate precautions should be taken.

The preparation of **12b** is outlined in the following experiments and is representative for the synthesis of compounds **12a**−**i**.

***trans*-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(5-methyl-2-thiopheneyl)-2-nitronaphthalene (9b) (R = Me).** A solution of 2-methylthiophene (**8b**) (0.97 mL, 10 mmol) in 10 mL of dry THF was cooled to −78 °C, treated with *n*-BuLi (4 mL, 2.5 M solution in hexanes, 10 mmol), and then stirred at −78 °C for 10 min and at 0 °C for 2.5 h. The solution was again cooled to −78 °C, and a solution of 2.30 g (10 mmol) of **7** in THF (10 mL) was added dropwise via cannula. Stirring was continued as the solution was allowed to warm to room temperature, and the reaction was then quenched with 100 mL of saturated NH_4Cl solution. The mixture was then extracted with CH_2Cl_2, which was dried over Na_2SO_4 and concentrated *in vacuo* to afford 3.04 g of crude product. This material was dissolved in 30 mL of acetonitrile treated with 0.75 mL (7 mmol) of triethylamine and stirred at room temperature for 16 h. The solution was concentrated, and the residue was purified by flash chromatography on silica gel, eluting with 15% ethyl acetate in hexanes, to afford 1.72 g (52% yield) of **9b**: ^{1}H NMR ($CDCl_3$) δ 6.74 (d, 1H, J = 3 Hz), 6.58 (s, 1H), 6.56 (dd, 1H, J = 1, 3 Hz), 6.52 (s, 1H), 4.95−4.84 (m, 2H), 3.87 (s, 3H), 3.72 (s, 3H), 3.0−2.85 (m, 2H), 2.5−2.4 (m, 2H), 2.42 (s, 3H).

***trans*-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(5-methyl-2-thiopheneyl)-2-naphthalenamine (10b).** To a suspension of **9b** (1.52 g, 4.5 mmol) in 40 mL of 95% ethanol and 12 mL of 6 N HCl was added 2.97 g (45 mmol) of Zn dust, added in four portions. The mixture was stirred at room temperature for 30 min and filtered and the filtrate concentrated to one-half the original volume and then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic extract was dried over Na_2SO_4 and concentrated to yield 1.35 g (99%) of **10b**: MS 304 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 6.70 (d, 1H, J = 3 Hz), 6.60 (bs, 2H), 6.46 (s, 1H), 3.88 (d, 1H, J = 8 Hz), 3.85 (s, 3H), 3.69 (s, 3H), 3.18 (m, 1H), 2.92−2.78 (m, 2H), 2.43 (s, 3H), 2.12−2.04 (m, 1H), 1.78−1.64 (m, 1H).

***trans*-9,10-Dimethoxy-2-methyl-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene (11b).** To a solution of 1.34 g of **10b** (44 mmol) in 45 mL of methanol was added 2.8 g (20.2 mmol) of K_2CO_3. The mixture was stirred for 15 min, then 396 mg (13.2 mmol) of paraformaldehyde was added, and the suspension was stirred at room temperature for 18 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in 100 g of trifluoroacetic acid, and the solution was stirred for 3 h, then concentrated to about 10 mL, and adjusted to a basic pH with aqueous $NaHCO_3$ solution. The mixture was extracted twice with CH_2Cl_2, and the combined extracts were washed with brine, then dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography, eluting with 4% MeOH:CH_2Cl_2, to afford 0.35 g (25% yield) of **11b**: MS 316 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 3H), 6.64 (s, 1H), 6.48 (s, 1H), 4.12−4.05 (m, 3H), 3.93 (s, 3H), 3.86 (s, 3H), 3.1−2.88 (m, 3H), 2.47 (s, 3H), 2.28 (m, 1H), 1.90 (m, 1H).

***trans*-2-Methyl-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol Hydrobromide (12b).** BBr_3 (3.3 mL, 1 M solution in CH_2Cl_2, 3.3 mmol) was added dropwise to a −78 °C solution of 260 mg (0.83 mmol) of **11b** in CH_2Cl_2 (5 mL). The reaction mixture was allowed to warm to 0 °C over a 2 h period and then stirred at that temperature for 2 h. The mixture was then cooled to −78 °C, and the reaction was quenched by the slow addition of MeOH (5 mL). The solution was then stirred at room temperature for 20 min and at reflux for 30 min and concentrated. The product was collected by triturating with CH_2Cl_2, filtering, and

drying to afford 274 mg of the title product (90% yield): mp 195−8 °C; MS 288 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 1.9 (m, 1H), 2.30 (m, 1H), 2.49 (s, 3H), 2.90 (m, 2H), 3.42 (m, 1H), 4.28 (d, 1H, J = 11 Hz), 4.35 (s, 2H), 6.62 (s, 1H), 6.68 (s, 1H), 7.30 (s, 1H). Anal. ($C_{16}H_{18}BrNO_2S$·0.3HBr) C,H,N.

The following compounds **12a**,**c**−**i** were prepared from **8a**,**c**−**i** using the same methodology as that described for **12b**.

***trans*-4,5,5a,6,7,11b-Hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (12a)**: MS 274 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 1.9−2.05 (m, 1H), 2.3−2.4 (m, 1H), 2.88−2.97 (m, 2H), 3.4−3.5 (m, 1H), 4.36 (d, 1H, J = 10 Hz), 4.46 (s, 2H), 6.62 (s, 1H), 7.02 (d, 1H, J = 6 Hz), 7.34 (s, 1H), 7.49 (d, 1H, J = 6 Hz). Anal. ($C_{15}H_{16}BrNO_2S$·0.2H_2O) C,H,N.

***trans*-2-Ethyl-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (12c)**: mp 154−5 °C; MS 302 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 1.32 (t, 3H, J = 7 Hz), 1.88−2.02 (m, 1H), 2.3−2.4 (m, 1H), 2.75−3.0 (m, 4H), 3.42 (dt, 1H, J = 5, 11 Hz), 4.29 (d, 1H, J = 11 Hz), 4.37 (s, 2H), 6.63 (s, 1H), 6.71 (s, 1H), 7.32 (s, 1H). Anal. ($C_{17}H_{20}BrNO_2S$) C,H,N.

***trans*-2-Propyl-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (12d)**: mp 183−6 °C; MS 316 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 1.0 (t, 3H, J = 7 Hz), 1.72 (sx, 2H, J = 7 Hz), 1.88−2.02 (m, 1H), 2.26−2.4 (m, 1H), 2.82 (t, 2H, J = 7 Hz), 2.92 (t, 2H, J = 6 Hz), 3.36−3.5 (m, 1H), 4.30 (d, 1H, J = 11 Hz), 4.36 (s, 2H), 6.62 (s, 1H), 6.71 (s, 1H), 7.32 (s, 1H); high-resolution MS calcd 316.1371, found 316.1384.

***trans*-2-Butyl-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (12e)**: mp 111−2 °C; MS 330 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 0.96 (t, 3H, J = 7 Hz), 1.35−1.45 (m, 2H), 1.58−1.76 (m, 2H), 1.9−2.0 (m, 1H), 2.05−2.2 (m, 1H), 2.7−3.0 (m, 4H), 3.41 (dt, 1H, J = 6 Hz), 4.28 (d, 1H, J = 11 Hz), 4.38 (s, 2H), 6.62 (s, 1H), 6.70 (s, 1H), 7.33 (s, 1H). Anal. ($C_{19}H_{24}BrNO_2S$·0.2H_2O).

***trans*-2-Hexyl-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (12f)**: mp 165−70 °C; MS 358 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 7.32 (s, 1H), 6.7 (s, 1H), 6.61 (s, 1H), 4.37 (s, 2H), 4.31 (d, J = 11 Hz, 1H), 3.42 (ddd, J = 6, 11, 11 Hz, 1H), 3.0−2.9 (m, 2H), 2.82 (t, J = 7 Hz, 2H), 2.4−2.3 (m, 1H), 2.05−1.9 (m, 1H), 1.72−1.6 (m, 2H), 1.4−1.2 (m, 6H), 0.94 (m, 3H).

***trans*-2-Cyclohexyl-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (12g)**: mp 195−6 °C; MS 356 $(M + H)^+$; high-resolution MS calcd for $C_{21}H_{26}NO_2S$ 356.1693, found 356.1684; ^{1}H NMR (CD_3OD) δ 1.35−1.50 (m, 6H), 1.7−2.1 (m, 5H), 2.26−2.4 (m, 1H), 2.91 (t, 2H, J = 6 Hz), 3.4 (dt, 1H, J = 4, 11 Hz), 4.38 (d, 1H, J = 11 Hz), 4.46 (s, 2H), 6.61 (s, 1H), 6.71 (s, 1H), 7.34 (s, 1H).

***trans*-2-(1-Cyclopentylmethyl)-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (12h)**: mp 180−5 °C; MS 356 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 7.34 (s, 1H), 6.71 (s, 1H), 6.64 (s, 1H), 4.38 (s, 2H), 4.29 (d, J = 11 Hz, 1H), 3.42 (ddd, J = 6, 11, 11 Hz, 1H), 3.0−2.8 (m, 2H), 2.83 (d, J = 8 Hz, 2H), 2.4−2.26 (m, 1H), 2.22−2.1 (m, 1H), 2.0−1.55 (m, 7H), 1.35−1.2 (m, 2H). Anal. ($C_{22}H_{26}BrClNO_2S$·0.15HBr·0.15EtOH) C,H,N.

***trans*-2-Chloro-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (12i)**: mp 261−3 °C; MS 308 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 7.18 (s, 1H), 6.95 (s, 1H), 6.52 (s, 1H), 4.39 (s, 2H), 4.33 (d, J = 11 Hz, 1H), 3.46 (ddd, J = 5, 11, 1 Hz, 1H), 2.95−2.88 (m, 2H), 2.4−2.27 (m, 1H), 2.05−1.85 (m, 1H). Anal. ($C_{15}H_{15}BrClNO_2S$·0.1H_2O) C,H,N.

5-(1,1-Dimethylethyl)-3-thiophenecarboxaldehyde (14). To a 0 °C solution of **13** (3.63 g, 32.4 mmol) in 60 mL of CH_2Cl_2 were added 9.17 g (80.9 mmol) of $AlCl_3$ and 2-methyl-2-bromopropane (4.66 g, 34 mmol). The solution was stirred at room temperature for 16 h and at reflux for 4 h, then cooled to room temperature, and poured into water. The mixture was made basic with aqueous $NaHCO_3$ and extracted with ether. The ethereal extract was washed with water, dried over $MgSO_4$, concentrated, and chromatographed on silica gel, eluting with 15:1 hexane:ethyl acetate, to afford 2.23 g (41%) of **14** as an oil: ^{1}H NMR (CD_3OD) δ 1.41 (s, 9H), 7.26 (d, 1H, J = 1 Hz), 8.2 (d, 1H, J = 1 Hz), 9.78 (s, 1H).

5-(1,1-Dimethylethyl)-3-thiophenecarboxaldehyde Ethylene Glycol Acetal (15). A flask fitted with a Dean−Stark trap was charged with a solution of 2.23 g (13.3 mmol) of **14**, 1.65 g (26.5 mmol) of ethylene glycol, and 25 mg of *p*-toluenesulfonic acid in 50 mL of cyclohexane (50 mL) and then heated at reflux for 12 h. The reaction mixture was cooled to room temperature and partitioned between saturated aqueous $NaHCO_3$ and ether. The ether layer was washed with water, dried over $MgSO_4$, and concentrated to afford 2.31 g (82% yield) of **15**: MS 213 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 4.86 (s, 4H), 5.72 (s, 1H), 6.87 (d, 1H, J = 1 Hz), 7.23 (d, 1H, J = 1 Hz).

2-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-nitronaphthyl)-5-(1,1-dimethylethyl)-3-thiophenecarboxaldehyde Ethylene Glycol Acetal (16). To a −78 °C solution of 1.49 g (7.0 mmol) of **15** in 10 mL of THF was added *n*-BuLi (2.8 mL, 2.5 M in hexane, 7.0 mmol), and the reaction mixture was stirred at −78 °C for 10 min and at 0 °C for 50 min. The solution was again cooled to −78 °C, and a solution of 1.50 g (6.4 mmol) of **7** in 15 mL of THF was added. The solution was stirred at −78 °C for 2 h and at −20 °C for 1 h. The reaction was quenched by the addition of saturated NH_4Cl solution, and then the mixture was partitioned between CH_2Cl_2 and water. The organic extract was washed with water, dried over $MgSO_4$, and concentrated. The crude product was dissolved in acetonitrile, treated with a catalytic amount of triethylamine, stirred for 16 h, and concentrated. The residue was chromatogaphed on silica gel to afford 369 mg (14% yield) of **16**: MS 448 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 2.4−2.5 (m, 2H), 2.8−3.0 (m, 2H), 3.73 (s, 3H), 3.87 (s, 3H), 3.95−4.05 (s, 2H), 4.1−4.2 (m, 2H), 5.05−5.1 (m, 1H), 5.35 (d, 1H, J = 6 Hz), 5.72 (s, 1H), 6.54 (s, 1H), 6.57 (s, 1H), 6.79 (s, 1H).

***trans*-9,10-Dimethoxy-2-(1,1-dimethylethyl)-4,5,5a,6,7,-11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene (11j).** To a solution of 390 mg (0.87 mmol) of **16** in 10 mL of a 3:1 mixture of acetic acid:water was added 570 mg of Zn dust, and the suspension was stirred at 60 °C for 15 min. The mixture was diluted with CH_2Cl_2 and water, made basic by the addition of saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, eluting with 85:5 CH_2Cl_2:methanol, to afford 63 mg (20% yield) of **11j**: MS 358 $(M + H)^+$; ^{1}H NMR (CD_3OD) δ 1.39 (s, 9H), 1.78−1.9 (m, 1H), 2.16−2.26 (m, 1H), 2.85−3.02 (m, 3H), 3.85 (s, 3H), 3.94 (s, 3H), 3.97 (d, 1H, J = 11 Hz), 4.06 (s, 2H), 6.54 (s, 1H), 6.64 (s, 1H), 7.47 (s, 1H).

***trans*-2-(1,1-Dimethylethyl)-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol Hydrobromide (12j).** Following the deprotection procedure described for the conversion of **11b** to **12b**, the title compound was prepared from **11j**: mp 202−4 °C dec; MS $(M + H)^+$ 330; ^{1}H NMR (CD_3OD) δ 1.41 (s, 9H), 1.9−2.0 (m, 1H), 2.26−2.4 (m, 1H), 2.85−2.95 (m, 2H), 3.35−3.48 (m, 1H), 4.28 (d, 1H, J = 11 Hz), 4.35 (s, 2H), 6.62 (s, 1H), 6.76 (s, 1H), 7.35 (s, 1H). Anal. ($C_{19}H_{24}BrNO_2S$·0.1HBr·0.1H_2O) C,H,N.

***cis*-4,5,5a,6,7,11b-Hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol Hydrobromide (17).** A solution of **11a** (72 mg, 0.24 mmol) in AcOH (3 mL) and 48% HBr (3 mL) was stirred at reflux for 2 h, then cooled to ambient temperature, and concentrated. Residual acetic acid was removed by azeotroping with heptane. The residue was dried overnight to give 83 mg (98%) of **17** as a tan solid: mp 193−4 °C dec; MS $(M + H)^+$ 274; ^{1}H NMR (CD_3OD) δ 7.37 (d, J = 6 Hz, 1H), 6.92 (d, J = 6 Hz, 1H), 6.89 (s, 1H), 6.57 (s, 1H), 4.42 (d, J = 6 Hz, 1H), 4.38 (d, J = 16 Hz, 1H), 4.29 (d, J = 16 Hz, 1H), 4.1 (m, 1H), 2.9−2.7 (m, 2H), 2.15−1.9 (m, 2H). Anal. ($C_{15}H_{16}BrNO_2S$·0.2HBr) C,H,N.

Representative Examples of the Preparation of Thiophenes 18a−n. Method A: 5-(3-Methylbutyl)-2-thiophenecarboxylic Acid, *N*-*tert*-Butylamide (18j). Isopentyl bromide (8 g, 53 mmol) was added to 53 mL of an ice-cooled solution of lithiothiophene (1.0 M in THF, 53 mmol). The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 16 h, then poured into water, and extracted with hexane. The organic layer was dried and concentrated,

and the residue was purified by column chromatography on silica gel, eluting with hexane, to give 7.2 g (88% yield) of 2-(3-methyl butyl)thiophene: ^{1}H NMR ($CDCl_3$) δ 7.10 (dd, J = 1, 6 Hz, 1H), 6.90 (dd, J = 4, 6 Hz, 1H), 6.78 (dd, J = 1, 4 Hz, 1H), 2.84 (t, J = 8 Hz, 2H), 1.7−1.5 (m, 3H), 0.94 (d, J = 6 Hz, 6H).

n-BuLi (13 mL, 2.5 M in hexanes, 32.4 mmol) was added to an ice cold solution of 2-(3-methylbutyl)thiophene (5 g, 32.4 mmol) in THF (50 mL), and the resulting solution was stirred at 0 °C for 1 h, then cooled to −78 °C, and treated with *tert*-butyl isocyanate (3.5 g, 35.6 mmol). The reaction mixture was allowed to warm up to 0 °C over 2 h; then the reaction was quenched with water and extracted with EtOAc. The extract was dried, concentrated, and purified via silica gel column chromatography eluting with 3:1 hexane:ethyl acetate to afford 6.4 g of **18j** as a white solid: MS 254 $(M + H)^+$, 271 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) δ 7.24 (d, J = 4 Hz, 1H), 6.72 (d, J = 4 Hz, 1H), 5.7 (bs, 1H), 2.82 (t, J = 8 Hz, 2H), 1.7−1.5 (m, 3H), 1.44 (s, 9H), 0.93 (d, J = 6 Hz, 6H).

Method B: 5-(1,1-Dimethylethyl)-2-thiophenecarboxylic Acid, *N*-*tert*-Butylamide (18g). To a 0 °C solution of 5.0 g (39.02 mmol) of **24** in 100 mL of CH_2Cl_2 were added 11 g (82.5 mmol) of $AlCl_3$ and 5.8 g (43.0 mmol) of *tert*-butyl bromide. The solution was stirred at room temperature for 18 h and then poured into 100 mL of ice water, and the mixture was extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and then concentrated to give 3.33 g (46%) of 5-*tert*-butyl-2-thiophenecarboxylic acid: MS $(M + H)^+$ 202; ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H), 6.89 (d, 1H, J = 4 Hz), 7.72 (d, 1H, J = 4 Hz).

A solution of this compound (3.1 g, 16.8 mmol) in $CHCl_3$ (60 mL) was treated with $SOCl_2$ (3.7 mL, 50.5 mmol), stirred at reflux for 4 h, and then concentrated. The residue was dissolved in $CHCl_3$ (60 mL), then treated with *tert*-butylamine (5.3 mL, 50.5 mmol), and stirred at reflux overnight. The reaction mixture was partitioned between CH_2Cl_2 and water, and the extract was washed with water and brine, dried, concentrated, and then purified via silica gel chromatography to yield 2.92 g (73%) of **18g**: MS 240 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 4 Hz, 1H), 6.78 (d, J = 4 Hz, 1H), 5.70 (bs, 1H), 1.45 (s, 9H), 1.39 (s, 9H).

Method C: 5-(3-Methylphenyl)-2-thiophenecarboxylic Acid, *N*-*tert*-Butylamide (18m). A −78 °C solution of 3-bromotoluene (5.8 g, 34 mmol) in THF (50 mL) was treated with *n*-BuLi (15 mL, 2.5 M in hexanes, 37 mmol), stirred at −78 °C for 30 min, and then treated with $B(OMe)_3$ (10.6 g, 102 mol). The reaction mixture was allowed to warm up to room temperature, stirred overnight, and then cooled in ice water and the reaction quenched with 2 N HCl. The mixture was extracted with CH_2Cl_2, washed with brine, dried, and concentrated to give 4.24 g (92% yield) of 3-methylphenylboronic acid.

A suspension of 907 mg (0.78 mmol) of $Pd(PPh_3)_4$ and **25** (5.09 g, 26.2 mmol) in 50 mL of DME was stirred at room temperature for 15 min and then treated with a solution of freshly prepared 3-methylphenylboronic acid (4.24 g, 31.2 mmol) in 10 mL of ethanol and 26 mL of 2 M aqueous Na_2CO_3. The reaction mixture was stirred at reflux for 24 h, then cooled to room temperature, diluted, and extracted with ether. The organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 5% ethyl acetate in hexane, to give 4.75 g (90% yield) of 5-(3-methylphenyl)-2-thiophenecarboxaldehyde: MS 203 $(M + H)^+$, 220 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1H), 7.74 (d, 1H, J = 5 Hz), 7.55−7.20 (m, 5H), 2.42 (s, 3H).

A solution of this compound (4.7 g, 23.3 mmol) was dissolved in 100 mL of ethanol and sequentially treated with a solution of $AgNO_3$ (7.9 g, 116.5 mmol) in 15 mL of water and a solution of KOH (6.5 g, 116.5 mmol) in 100 mL of water. The suspension was stirred at room temperature for 1 h and then filtered, and the filter cake was washed with water and ether. The filtrate was separated, and the aqueous layer was acidified with concentrated HCl to pH 4 and extracted twice with ether. The ethereal extract was dried over $MgSO_4$ and concentrated to give 4.6 g (96% yield) of 5-(3-methylphenyl)-2-thiophenecarboxylic acid: MS 236 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) δ 7.86 (d, 1H, J = 5 Hz), 7.5−7.4 (m, 2H), 7.35−7.10 (m, 3H), 2.4 (s, 3H). This compound was converted to **18m** following the procedures described for the preparation of **18g**.

The general procedure for preparing compounds **23a**−**n** is illustrated below for the synthesis of **23j**.

3-(6,7-Dimethoxy-2-nitro-1,2,3,4-tetrahydro-1-naphthyl)-5-(3-methylbutyl)-2-thiophenecarboxylic Acid, *N*-*tert*-Butylamide (19j). A 0 °C solution of **18j** (2.3 g, 9.1 mmol) in THF (20 mL) was treated with *n*-BuLi (7.3 mL, 2.5 M in hexane, 18.2 mmol), stirred at 0 °C for 1 h, then cooled to −78 °C, and treated with a precooled (−78 °C) solution of **7** (2.1 g, 9.1 mmol) in THF (20 mL). The reaction mixture was stirred at −78 °C for 1.5 h and then at 0 °C for 45 min and then the reaction quenched with saturated NH_4Cl. The mixture was extracted twice with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$ and concentrated. The residue was dissolved in acetonitrile (50 mL), treated with Et_3N (0.3 mL), and stirred overnight. The reaction mixture was concentrated and purified via column chromatography eluting with 8:1 hexane:ethyl acetate to give 2.7 g (61%) of **19j**: MS 489 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 6.58 (s, 1H), 6.36 (s, 1H), 6.30 (s, 1H), 5.71 (bs, 1H), 5.47 (d, J = 9 Hz, 1H), 5.05 (m, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.05−2.85 (m, 2H), 2.68 (t, J = 9 Hz, 2H), 2.5−2.35 (m, 2H), 1.6−1.45 (m, 3H), 1.42 (s, 9H), 0.91 (d, J = 6 Hz, 3H), 0.90 (s, J = 6 Hz, 3H).

3-(2-Amino-6,7-dimethoxy-1,2,3,4-tetrahydro-1-naphthyl)-5-(3-methylbutyl)-2-thiophenecarboxylic Acid, *N*-*tert*-Butylamide (20j). Following the procedure described for the reduction of **9b** to **10b**, **19j** (2.7 g, 5.5 mmol) was converted to **20j** (1.88 g, 75% yield): MS 459 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 6.60 (s, 1H), 6.30 (s, 1H), 6.20 (s, 1H), 4.51 (d, J = 10 Hz, 1H), 3.86 (s, 3H), 3.64 (s, 3H), 3.36−3.25 (m, 1H), 3.1−2.8 (m, 2H), 2.70 (t, J = 9 Hz, 2H), 2.3−2.2 (m, 1H), 2.0−1.85 (m, 1H), 1.7−1.5 (m, 3H), 1.42 (s, 9H), 0.89 (d, J = 6 Hz, 3H), 0.88 (d, J = 6 Hz, 3H).

***trans*-2-(3-Methylbutyl)-4,5,5a,6,7,11b-hexahydro-3-thia-4-oxo-5-aza-9,10-dimethoxycyclopent-1-ena[*c*]phenanthrene (21j).** To a solution of 1.87 g (4.1 mmol) of **20j** in 100 mL of toluene was added *p*-TsOH·H_2O (1.55 g, 8.2 mmol), and the reaction mixture was stirred at reflux for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with aqueous $NaHCO_3$, H_2O, and brine, then dried over Na_2SO_4, and concentrated under vacuum. The crude product was crystallized from ethanol to give 0.91 g (60% yield) of **21j** as a white solid: MS 386 $(M + H)^+$, 403 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) δ 7.14 (s, 1H), 7.13 (s, 1H), 6.67 (s, 1H), 5.95 (s, 1H), 4.14 (d, J = 12 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.75 (ddd, J = 3, 12, 12 Hz, 1H), 3.0−2.76 (m, 4H), 2.1−1.9 (m, 2H), 1.7−1.55 (m, 3H), 0.95 (d, J = 6 Hz, 6H).

***trans*-2-(3-Methylbutyl)-4,5,5a,6,7,11b-hexahydro-3-thia-5-aza-9,10-dimethoxycyclopent-1-ena[*c*]phenanthrene (22j).** A suspension of **21j** (0.91 g, 2.3 mmol) in THF (12 mL) was treated with BH_3·THF (12 mL, 1 M solution in THF, 12 mmol) resulting in a clear solution which was then stirred at reflux for 14 h. The reaction mixture was cooled in an ice bath and then the reaction quenched with 10 mL of a ca. 1 M solution of anhydrous HCl in MeOH. After being stirred at reflux for 4 h, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2 twice. The combined organic extracts were washed with water and brine, dried, and concentrated. The residue was purified via silica gel chromatography to afford 0.85 g (97%) of **22j** as a white solid: mp 110−2 °C; MS 372 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.0 (s, 1H), 6.89 (s, 1H), 6.72 (s, 1H), 4.05 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.56 (d, J = 11 Hz, 1H), 3.0−2.6 (m, 5H), 2.3−2.15 (m, 1H), 1.8−1.5 (m, 4H), 0.95 (d, J = 6 Hz, 6H). Anal. ($C_{22}H_{29}NO_2S$) C,H,N.

***trans*-2-(3-Methylbutyl)-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol Hydrobromide (23j).** Following the procedure described for the preparation of **12b**, **22j** (484 mg, 1.3 mmol) was deprotected with BBr_3 (5.2 mL, 1 M solution in CH_2Cl_2) to afford 426 mg of **23j**: mp 73−5 °C; MS 344 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 1H), 6.98 (s, 1H), 6.67 (s, 1H), 4.45 (s, 2H), 4.0 (d, J = 11 Hz, 1H), 3.28−3.15 (m, 1H), 3.0−2.8 (m, 4H), 2.4−2.25 (m, 1H), 2.0−1.8 (m, 2H), 1.7−1.58 (n, 2H), 0.98 (d, J = 6 Hz, 6H). Anal. ($C_{20}H_{26}BrNO_2S$·0.5H_2O) C,H,N.

The following compounds **23a**−**n** were prepared from **18a**−**n** following the procedures described for **23j**.

***trans*-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*] phenanthrene-9,10-diol hydrobromide (23a)**: mp 185 °C; MS 274 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 7.59 (d, 1H, J = 3 Hz), 7.32 (d, 1H, J = 3 Hz), 6.88 (s, 1H), 4.58 (d, 1H, J = 8 Hz), 4.52 (d, 1H, J = 8 Hz), 4.10 (d, 1H, J = 6 Hz), 3.25 (m, 1H), 2.98 (m, 1H), 2.84 (m, 1H), 2.37 (m, 1H), 1.96 (m, 1H). Anal. ($C_{15}H_{16}BrNO_2S$·0.2HBr) C,H,N.

***trans*-2-Methyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23b)**: mp 223−5 °C; MS 288 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 7.0 (s, 1H), 6.89 (s, 1H), 6.68 (s, 1H), 4.4 (s, 2H), 4.01 (d, 1H, J = 11 Hz), 3.20 (m, 1H), 3.02−2.80 (m, 2H), 2.35 (s, 3H), 2.45−2.20 (m, 1H), 2.0−1.85 (m, 1H). Anal. ($C_{16}H_{18}BrNO_2S$·0.2HBr) C,H,N.

***trans*-2-Ethyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23c):** mp 235−6 °C; MS 302 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 7.20 (s, 1H), 6.90 (s, 1H), 6.67 (s, 1H), 4.46 (s, 2H), 4.02 (d, 1H, J = 11 Hz), 3.2 (m, 1H), 3.0−2.8 (m, 4H), 2.40−2.28 (m, 1H), 2.20−1.86 (m, 1H), 1.36 (t, 3H, J = 7 Hz). Anal. ($C_{17}H_{20}BrNO_2S$·0.10HBr) C,H,N.

***trans*-2-Propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23d)**: mp 133−4 °C; MS 316 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 1.03 (t, 3H, J = 8 Hz), 1.75 (sx, 2H, J = 8 Hz), 1.9−2.0 (m, 1H), 2.28−2.41 (m, 1H), 2.87 (t, 2H, J = 8 Hz), 2.88−3.05 (m, 2H), 3.15−3.27 (m, 1H), 4.02 (d, 1H, J = 11 Hz), 4.46 (s, 2H), 6.67 (s, 1H), 6.90 (s, 1H), 7.02 (s, 1H). Anal. ($C_{18}H_{22}BrNO_2S$·0.3H_2O) C,H,N.

***trans*-2-Butyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23e)**: mp 152−3 °C; MS 330 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 0.98 (t, 3H, J = 7 Hz), 1.35−1.5 (m, 2H), 1.6−1.8 (m, 2H), 1.85−2.0 (m, 1H), 2.26−2.4 (m, 1H), 2.76−3.05 (m, 4H), 3.16−3.26 (m, 1H), 4.01 (d, 1H, J = 11 Hz), 4.46 (s, 2H), 6.67 (s, 1H), 6.89 (s, 1H), 7.02 (s, 1H). Anal. ($C_{19}H_{24}BrNO_2S$·0.6H_2O) C,H,N.

***trans*-2-Pentyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23f)**: mp 78−80 °C; MS 344 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 7.01 (s, 1H), 6.89 (s, 1H), 6.66 (s, 1H), 4.46 (bs, 2H), 4.02 (d, J = 11 Hz, 1H), 3.3−3.15 (m, 1H), 3.05−2.8 (m, 4H), 2.4−2.3 (m, 1H), 2.0−1.9 (m, 1H), 1.8−1.65 (m, 2H), 1.5−1.3 (m, 4H), 0.94 (t, J = 6 Hz, 3H). Anal. ($C_{20}H_{26}BrNO_2S$·0.8H_2O·0.1HBr) C,H,N.

***trans*-2-(1,1-Dimethylethyl)-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23g)**: mp 197−8 °C; MS 330 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 1.46 (s, 9H), 1.86−2.02 (m, 1H), 2.29−2.43 (m, 1H), 2.78−3.04 (m, 2H), 3.16−3.28 (m, 1H), 4.02 (d, 1H, J = 11 Hz), 4.46 (s, 2H), 6.68 (s, 1H), 6.88 (s, 1H), 7.03 (s, 1H). Anal. ($C_{19}H_{24}BrNO_2S$·0.6H_2O) C,H,N.

***trans*-2-(2-Propyl)-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23h)**: mp 186−7 °C; MS 316 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 1.39 (d, 6H, J = 7 Hz), 1.87−2.02 (m, 1H), 2.28−2.43 (m, 1H), 2.8−3.28 (m, 4H), 4.03 (d, 1H, J = 11 Hz), 4.47 (s, 2H), 6.68 (s, 1H), 6.89 (s, 1H), 7.03 (s, 1H). Anal. ($C_{18}H_{22}BrNO_2S$·0.4H_2O) C,H,N.

***trans*-2-(2-Methylpropyl)-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23i)**: mp 164−5 °C; MS 330 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 0.98 (d, 3H, J = 7 Hz), 1.01 (d, 3H, J = 7 Hz), 1.01 (d, 3H, J = 7 Hz), 1.85−2.0 (m, 2H), 2.27−2.4 (m, 1H), 2.75 (d, 2H, J = 7 Hz), 2.8−3.05 (m, 2H), 3.15−3.28 (m, 1H), 4.02 (d, 1H, J = 11 Hz), 4.48 (s, 2H), 6.67 (s, 1H), 6.89 (s, 1H), 7.00 (s, 1H). Anal. ($C_{19}H_{24}BrNO_2S$·0.1HBr) C,H,N.

***trans*-2-Cyclohexyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23k)**: mp 191−2 °C; MS 356 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 1.2−1.5 (m, 6H), 1.7−2.2 (m, 5H), 2.28−2.4 (m, 1H), 2.8−3.04 (m, 2H), 3.15−3.3 (m, 1H), 4.02 (d, 1H, J = 11 Hz), 4.46 (s, 2H), 6.67 (s, 1H), 6.89 (s, 1H), 7.02 (s, 1H). Anal. ($C_{21}H_{26}BrNO_2S$·0.1H_2O·0.2HBr) C,H,N.

***trans*-2-Phenyl-4,5,5a,6,7,11b-Hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23l)**: mp 204−5 °C; MS 350 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 1.9−2.05 (m, 1H), 2.32−2.44 (m, 1H), 2.8−3.06 (m, 2H), 3.2−3.3 (m, 1H), 4.12 (d, 1H, J = 11 Hz), 4.52 (d, 1H, J = 15 Hz), 4.60 (d, 1H, J = 15 Hz), 6.68 (s, 1H), 6.97 (s, 1H), 7.3−7.5 (m, 3H), 7.58 (s, 1H), 7.66−7.75 (m, 2H). Anal. ($C_{21}H_{20}BrNO_2S$·0.2HBr) C,H,N.

2-(3-Methylphenyl)-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (23m): mp 214−5 °C; MS 364 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 7.6−7.4 (m, 2H), 7.32 (t, 1H, J = 7 Hz), 7.16 (d, 1H, J = 7 Hz), 6.97 (s, 1H), 6.68 (s, 1H), 4.56 (m, 2H), 4.10 (d, 1H, J = 11 Hz), 3.3−3.2 (m, 1H), 3.1−2.8 (m, 2H), 2.40 (s, 3H), 2.4−2.2 (m, 1H), 2.05−1.9 (m, 1H). Anal. ($C_{22}H_{22}BrNO_2S$·0.2HBr) C,H,N.

***trans*-2-Chloro-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol hydrobromide (23n)**: mp 255−7 °C; MS 308 (M + H)$^+$; ^{1}H NMR (CD_3OD) δ 7.24 (s, 1H), 6.81 (s, 1H), 6.67 (s, 1H), 4.52−4.40 (m, 2H), 4.04 (d, J = 11 Hz, 1H), 3.30−3.18 (m, 1H), 3.02−2.77 (m, 2H), 2.40−2.28 (m, 1H), 2.00−1.85 (m, 1H). Anal. ($C_{15}H_{15}BrClNO_2S$) C,H,N.

3-Thiophenecarboxylic Acid, *N*,*N*-Diethylamide (26). A solution of 3-thiophenecarboxylic acid (5.0 g, 39 mmol) in $CHCl_3$ (20 mL) was treated with 10 mL (134 mmol) of $SOCl_2$. After being stirred at reflux for 3 h, the reaction mixture was concentrated, redissolved in 15 mL of CH_2Cl_2, cooled in an ice bath, and then treated with Et_2N (13 mL, 126 mmol). The reaction mixture was stirred at room temperature for 1 h. Water was added, and the mixture was extracted with CH_2Cl_2, which was washed with aqueous $NaHCO_3$ solution, water, and brine, concentrated, and purified by flash chromatography on silica gel, eluting with 6:1 hexane:ethyl acetate, to afford 6.34 g (89%) of **26**: ^{1}H NMR ($CDCl_3$) δ 7.48 (dd, 1H, J = 1, 3 Hz), 7.32 (dd, 1H, J = 3, 6 Hz), 7.20 (dd, 1H, J = 1, 6 Hz), 3.60−3.30 (bs, 4H), 1.20 (bm, 6H).

2-(Trimethylsilyl)-3-thiophenecarboxylic Acid, *N*,*N*-Diethylamide (27). To a −78 °C solution of 3 g (16.4 mmol) of **26** in 20 mL of THF was added 1.68 g (2.1 mL, 16.4 mmol) of TMEDA followed by 12.6 mL of a 1.3 M solution of *s*-BuLi in cyclohexane (16.4 mmol), and the reaction mixture was stirred for 1 h. Chlorotrimethylsilane (2.1 mL, 16.4 mmol) was added, and the solution was stirred for 45 min and then poured into 100 mL of water. The mixture was extracted three times with CH_2Cl_2, and the solvent was washed with brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography, eluting with 3:1 hexane:ethyl acetate, to afford 1.4 g (38% yield) of **27**: MS 256 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 1H, J = 5 Hz), 7.10 (d, 1H, J = 5 Hz), 3.60−3.50 (bm, 2H), 3.3−3.10 (bm, 2H), 1.30−1.20 (bm, 3H), 1.15−1.05 (bm, 3H), 0.34 (s, 9H).

***trans*-4-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-nitronaphthalen-1-yl)-2-(trimethylsilyl)-3-thiophenecarboxylic Acid, *N*,*N*-Diethylamide (28).** To a −78 °C solution of **27** (1.4 g, 5.49 mmol) in 15 mL of THF was added TMEDA (0.7 mL, 5.5 mmol) followed by *s*-BuLi (4.2 mL, 1.3 M in cyclohexane, 5.5 mmol), and the reaction mixture was stirred for 40 min. To this solution was added a solution of 1.30 g of **7** (5.49 mmol) in 20 mL of THF, and the reaction mixture was stirred at −78 °C for 1 h and at −20 °C for 1.5 h; then the reaction was quenched by the addition of saturated NH_4Cl. The mixture was diluted with water and extracted with CH_2Cl_2. The solvent layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in 50 mL of acetonitrile, 1 mL of triethylamine was added, and the reaction mixture was stirred for 16 h. The solvent and amine were removed by evaporation, and the residue was purified by flash chromatography over silica gel to afford 554 mg (20%) of **28**.

***trans*-9,10-Dimethoxy-4,5,5a,6,7,11b-hexahydro-4-oxo-2-thia-5-azacyclopent-3-ena[*c*]phenanthrene (29).** To a solution of 554 mg (1.13 mmol) of **28** in 8 mL of ethanol and 3 mL of 6 N HCl was added 700 mg of Zn dust, and the mixture was stirred for 15 min. The mixture was diluted with 20 mL of CH_2Cl_2 and then filtered. The organic layer of the filtrate was separated. The aqueous layer was adjusted to pH 10 and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4,

filtered, and concentrated. The residue was dissolved in 7 mL of methanol, 3 mL of 6 N HCl was added, and the solution was stirred for 4 h. The methanol was evaporated off, and the residue was dissolved in 6 mL of water, which was then extracted with ether. The aqueous layer was adjusted to pH 10 and extracted with ethyl acetate. Removal of the solvent gave 256 mg (66%) of *trans*-4-(2-amino-1,2,3,4-tetrahydro-6,7-dimethoxynaphthalen-1-yl)-3-thiophenecarboxylic acid, *N*,*N*-diethylamide.

To a solution of 240 mg (0.6 mmol) of this compound in 10 mL of toluene was added 2 mL of trimethylaluminum, and the solution was heated at reflux for 2 h. The solution was cooled to room temperature, and the reaction was quenched by addition of $Na_2SO_4 \cdot 10H_2O$ followed by addition of K_2CO_3 and stirring for 20 min. The mixture was filtered, and the filtrate was evaporated. The residue was dissolved in ethyl acetate and washed with saturated Na_2CO_3 and brine. The solvent was removed, and the material was purified by flash chromatography on silica gel, eluting with 100:5:0.5 CH_2Cl_2:EtOH:NH_4OH, to afford 170 mg (90%) of **29**: MS 316 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 7.53 (d, 1H, $J = 6$ Hz), 7.36 (s, 1H), 7.17 (d, 1H, $J = 6$ Hz), 6.65 (s, 1H), 5.75 (bs, 1H), 4.49 (d, 1H, $J = 12$ Hz), 3.98 (s, 3H), 3.88 (s, 3H), 3.80 (dd, 1H, $J = 4$, 12 Hz), 3.15−2.80 (m, 2H), 2.10−1.95 (m, 2H).

***trans*-9,10-Dimethoxy-4,5,5a,6,7,11b-hexahydro-2-thia-5-azacyclopent-3-ena[*c*]phenanthrene (30).** A sample (170 mg, 0.54 mmol) of **29** was reduced to **30** (74 mg, 46%) following the procedure described for the conversion of **21j** to **22j**: MS 302 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 7.48 (s, 1H), 7.20 (d, 1H, $J = 6$ Hz), 6.84 (d, 1H, $J = 6$ Hz), 6.67 (s, 1H), 4.14 (s, 2H), 3.98 (d, 1H, $J = 9$ Hz), 3.95 (s, 3H), 3.88 (s, 3H), 3.0−2.8 (m, 3H), 2.22−2.14 (m, 1H), 1.9−1.78 (m, 1H).

***trans*-4,5,5a,6,7,11b-Hexahydro-2-thia-5-azacyclopent-3-ena[*c*]phenanthrene-9,10-diol Hydrobromide (31).** Following the procedure described for the deprotection of **11b** to **12b**, **30** (74 mg, 0.24 mmol) was converted to 81 mg (90%) of **31**: MS 274 $(M + H)^+$; ^1H NMR (CD_3OD) δ 7.38 (d, 1H, $J = 6$ Hz), 6.92 (d, 1H, $J = 6$ Hz), 6.90 (s, 1H), 6.58 (s, 1H), 4.45−4.20 (m, 3H), 4.10 (m, 1H), 3.0−2.8 (m, 2H), 2.2−1.95 (m, 2H). Anal. ($C_{15}H_{16}BrNO_2S \cdot 0.30HBr$) C,H,N.

4-Bromo-2-propyl-3-thiophenecarboxaldehyde (34). To a solution of diisopropylamine (2.7 mL, 19.4 mmol) in 50 mL of THF cooled to −78 °C was added 7.8 mL (2.5 M in hexane, 19.4 mmol) of *n*-butyllithium, and the reaction mixture was stirred for 0.5 h. To the solution was added 4.7 g (19.4 mmol) of 3,4-dibromothiophene (**32**); then the reaction mixture was stirred for 1 h at −78 °C. Iodopropane (2.8 mL, 29.1 mmol) was then added; the reaction mixture was stirred for 10 min at −78 °C and then stirred for 2 h at room temperature. The reaction was quenched with aqueous saturated NH_4Cl, extracted with ether, washed with H_2O and brine, and concentrated to give 5.27 g of crude **33**. This compound (5.25 g, 18.5 mmol) was dissolved in 80 mL of ether and cooled to −78 °C. *n*-BuLi (7.4 mL, 18.5 mmol) was added dropwise via syringe, and the resulting mixture was stirred at −78 °C for 20 min. DMF was added (1.86 mL, 24.03 mmol), and the reaction mixture was stirred at −78 °C for 1 h, then poured into water, and extracted with ether. The extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Silica gel column chromatography afforded 0.63 g (15%) of **34**: ^1H NMR ($CDCl_3$) δ 10.07 (s, 1H), 7.09 (s, 1H), 3.20 (t, $J = 7$ Hz, 2H), 1.74 (m, 2H), 1.02 (t, $J = 7$ Hz, 3H).

4-Bromo-3-[(methoxymethoxy)methyl]-2-propylthiophene (35). A solution of **34** (850 mg, 3.6 mmol) in 20 mL of EtOH was treated with 206 mg (5.4 mmol) of $NaBH_4$. The mixture was stirred at room temperature for 1 h; then the reaction was quenched with water and extracted with ether. The extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to give 950 mg of an oil which was dissolved in 20 mL of CH_2Cl_2 and then treated with 1.4 mL (8.1 mmol) of diisopropylethylamine and 0.46 mL (6 mmol) of chloromethyl methyl ether. The reaction mixture was stirred at room temperature for 16 h, diluted with ether, washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel, eluting with 20:1 hexane:ethyl acetate, to afford 754 mg (75%) of **35**: ^1H NMR ($CDCl_3$) δ 7.09 (s, 1H), 4.69 (s, 2H), 4.52 (s, 2H), 3.44 (s, 3H), 2.88−2.82 (m, 2H), 1.75−1.62 (m, 2H), 0.99 (t, $J = 7$ Hz, 3H).

4-(6,7-Dimethoxy-2-nitro-1,2,3,4-tetrahydronaphth-1-yl)-3-[(methoxymethoxy)methyl]-2-propylthiophene (36). A −78 °C solution of **35** (0.75 g, 2.7 mmol) in ether (20 mL) was treated with *n*-BuLi (1.07 mL, 2.5 M in hexane, 2.7 mmol), stirred at −78 °C for 0.5 h, and then treated with a precooled solution of **7** (0.63 g, 2.7 mmol) in THF (10 mL). The reaction mixture was stirred at −78 °C for 1 h, gradually turning into a suspension, and at 0 °C for 0.5 h, after which the reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was dissolved in CH_3CN, treated with Et_3N, stirred overnight, concentrated, and purified via silica gel column chromatography to afford 0.67 g (57%) of **36**: MS 453 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 6.59 (s, 1H), 6.56 (s, 1H), 6.39 (s, 1H), 5.2−5.15 (m, 1H), 4.91 (d, $J = 6$ Hz, 1H), 4.63 (d, $J = 6$ Hz, 1H), 4.58 (d, $J = 6$ Hz, 1H), 4.48 (d, $J = 11$ Hz, 1H), 4.35 (d, $J = 11$ Hz, 1H), 3.86 (s, 3H), 3.68 (s, 3H), 3.37 (s, 3H), 2.95−2.85 (m, 2H), 2.81 (t, $J = 7$ Hz, 2H), 2.5−2.3 (m, 2H), 1.68 (sx, $J = 7$ Hz, 2H), 0.97 (t, $J = 7$ Hz, 3H).

9,10-Dimethoxy-3-propyl-4,5,5a,6,7,11b-hexahydro-2-thia-5-azacyclopent-3-ena[*c*]phenanthrene (38). To a solution of **36** (0.38 g, 0.9 mmol) in 6 mL of EtOH and 1 mL of 6 M HCl was added Zn (0.6 g, 9 mmol). After being stirred at room temperature, the reaction mixture was filtered, and the filtrate was concentrated and partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was dried, concentrated, and then dissolved in 10 mL of THF, 0.5 mL of 12 N HCl was added, and the mixture was stirred at reflux for 1.5 h. Removal of the solvent gave the intermediate chloro compound **37**, which was immediately dissolved in *tert*-butyl alcohol, treated with Na_2CO_3 (1.0 g, 7.1 mmol), and stirred at reflux for 30 min. The mixture was cooled to room temperature, poured into water, and extracted with CH_2Cl_2. The solvent was dried and removed by evaporation. The residue was purified by silica gel chromatography, eluting with CH_2Cl_2:methanol 97:3, to afford 184 mg (62% overall) of **38**: MS 344 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 7.23 (s, 1H), 7.10 (d, $J = 1$ Hz, 1H), 6.80 (s, 1H), 4.13 (d, $J = 15$ Hz, 1H), 3.95 (d, $J = 15$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.71 (d, $J = 11$ Hz, 1H), 3.60−3.52 (m, 1H), 2.88 (t, $J = 7$ Hz, 2H), 2.75−2.65 (m, 2H), 2.22−2.10 (m, 1H), 1.9−1.6 (m, 3H), 1.0 (t, $J = 7$ Hz, 3H).

3-Propyl-4,5,5a,6,7,11b-hexahydro-2-thia-5-azacyclopent-3-ena[*c*]phenanthrene-9,10-diol Trifluoroacetate Salt (39). Following the procedures described for the preparation of **12b**, **38** was reacted with BBr_3 to give **39** as a 1:1 mixture of *cis*:*trans* isomers. The mixture was purified by reverse phase HPLC, eluting with 1:1 methanol:0.1% TFA to give the *trans* isomer: mp 114−6 °C; MS 316 $(M + H)^+$; ^1H NMR (CD_3OD) δ 7.27 (d, $J = 1$ Hz, 1H), 7.11 (s, 1H), 6.64 (s, 1H), 4.43 (d, $J = 14$ Hz, 1H), 4.34 (d, $J = 14$ Hz, 1H), 4.10 (d, $J = 11$ Hz, 1H), 3.14 (td, $J = 11$, 6 Hz, 1H), 2.9−2.75 (m, 4H), 2.35−2.24 (m, 1H), 2.0−1.85 (m, 1H), 1.71 (sx, $J = 7$ Hz, 2H), 1.02 (t, $J = 7$ Hz, 3H); high-resolution MS calcd for $C_{18}H_{22}NO_2S$ $(M + H)^+$ 316.1371, found 316.1374.

3-Bromo-4-propylthiophene (40). A solution of 3,4-dibromothiophene (**32**) (15.3 g, 63.3 mmol) in 50 mL of ether was cooled to −78 °C and treated with *n*-BuLi (25.3 mL, 2.5 M solution in hexanes, 66.5 mmol). While holding the temperature at −78 °C, the reaction mixture was stirred for 15 min, then 7.8 g (66.5 mmol) of *N*-methyl-*N*-methoxypropionamide was added to the resulting suspension, and the reaction mixture was stirred for 1 h. The reaction was quenched with saturated NH_4Cl, and the mixture was diluted with ether. The ether layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from hexanes to give 7.7 g (53%) of 3-bromo-4-(1-oxopropyl)thiophene: MS 236, 238 $(M + NH_4)^+$; ^1H NMR ($CDCl_3$) δ 7.99 (d, $J = 3$ Hz, 1H), 7.32 (d, $J = 3$ Hz, 1H), 2.98 (q, $J = 7$ Hz, 2H), 1.21 (t, $J = 7$ Hz, 3H).

This compound was dissolved in diethylene glycol (100 mL), treated with KOH (5.9 g, 0.1 mol) and hydrazine (4.4 g, 2.7 mmol), stirred at reflux for 16 h, and then partitioned between 3 M HCl and pentane. The extract was washed with brine, dried, and concentrated to afford 4.75 g (66%) of **40**: ^1H NMR

($CDCl_3$) δ 7.22 (d, J = 3 Hz, 1H), 6.95 (d, J = 3 Hz, 1H), 2.56 (t, J = 7.5 Hz, 2H), 1.65 (sextet, J = 7.5 Hz, 2H). 0.98 (t, J = 7.5 Hz, 3H).

1-(3-Bromo-4-propyl-2-thiopheneyl)-1,2,3,4-tetrahydro-6,7-(methylenedioxy)-2-nitronaphthalene (42). A solution of **40** (2.0 g, 9.1 mmol) in THF (5 mL) was added to a −78 °C solution of freshly prepared LDA (prepared be reacting *n*-BuLi (3.9 mL, 2.5 M in hexanes, 9.8 mmol) with diisopropylamine (0.99 g, 9.8 mmol) for 0.5 h at −78 °C). The reaction mixture was stirred at −78 °C for 1 h, then treated with a solution of **41** (2.24 g, 9.8 mmol) in THF (12 mL), and stirred for an additional 1.5 h, after which the reaction was quenched with saturated aqueous NH_4Cl. After being extracted with ether, washed with brine, dried, and concentrated, the residue was dissolved in CH_3CN treated with Et_3N (ca. 2 mL), stirred overnight, concentrated, and directly purified via column chromatography to afford 0.72 g (20%) of **42**: ^{1}H NMR ($CDCl_3$) δ 6.93 (s, 1H), 6.58 (s, 1H), 6.38 (s, 1H), 5.91 (s, 2H), 5.18 (d, J = 7 Hz, 1H), 5.05−4.95 (m, 1H), 3.0−2.8 (m, 2H), 2.6−2.4 (m, 4H), 1.7−1.55 (m, 2H), 1.0 (t, J = 8 Hz, 3H).

1-(4-Propyl-2-thiopheneyl)-1,2,3,4-tetrahydro-6,7-(methylenedioxy)-2-naphthylamine (43). Following the procedure described for the reduction of **9b** to **10b**, compound **42** (1.25 g, 2.95 mmol) was converted to 0.91 g (84%) of 1-(3-bromo-4-propyl-2-thiopheneyl)-1,2,3,4-tetrahydro-6,7-(methylenedioxy)-2-naphthylamine: MS 394, 396 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1H), 6.57 (s, 1H), 6.28 (s, 1H), 5.87 (s, 2H), 4.22 (d, J = 9 Hz, 1H), 3.33−3.23 (m, 1H), 3.0−2.8 (m, 2H), 2.62−2.55 (m, 2H), 2.15−2.05 (m, 1H), 1.82−1.6 (m, 3H), 1.02 (t, J = 7 Hz, 3H).

A solution (0.78 g, 2.0 mmol) of this compound in ethanol was hydrogenated at 4 atm of H_2 with 0.3 g of 10% Pd/C catalyst. The catalyst was removed by filtration, and the filtrate was concentrated to give 0.63 g (100%) of **43**: ^{1}H NMR ($CDCl_3$) δ 6.81 (s, 1H), 6.77 (s, 1H), 6.56 (s, 1H), 6.41 (s, 1H), 5.87 (s, 2H), 3.90 (d, J = 8 Hz, 1H), 3.25−3.15 (m, 1H), 2.92−2.78 (m, 2H), 2.54 (t, J = 7 Hz, 2H), 2.13−2.05 (m, 1H), 1.8−1.6 (m, 3H), 0.96 (t, J = 7 Hz, 3H).

***trans*-3-Propyl-4,5,5a,6,7,11b-hexahydro-1-thia-5-azacyclopent-2-ena[*c*]phenanthrene-9,10-diol Hydrochloride (45).** Following the procedures described for the preparation of **11b** from **10b**, **45** (0.85 g, 2.7 mmol) was converted to 0.4 g (45%) of a 1.5:1 mixture of *cis*:*trans* **44**. Pure *trans* isomer (0.07 g, 0.21 mmol; isolated via silica gel column chromatography) was dissolved in CH_2Cl_2 (5 mL), cooled to 0 °C, and then treated with BCl_3 (2 mL, 1 M in CH_2Cl_2, 2 mmol). After being stirred for 2 h at 0 °C, the reaction was quenched with MeOH, stirred at room temperature for 2 h, concentrated, and triturated with ether. The precipitate was collected and dried to give 0.08 g (99%) of **45**: mp > 170 °C dec; HRMS calcd for $C_{18}H_{22}NO_2S$ 316.1371, found 316.1365; ^{1}H NMR (CD_3OD) δ 7.35 (s, 1H), 7.13 (s, 1H), 6.63 (s, 1H), 4.36 (s, 2H), 4.33 (d, J = 11 Hz, 1H), 3.50−3.35 (m, 1H), 3.0−2.85 (m, 2H), 2.52 (t, J = 7 Hz, 2H), 2.40−2.28 (m, 1H), 2.04−1.90 (m, 1H), 1.67 (sextet, J = 7 Hz, 2H), 0.99 (t, J = 7 Hz, 3H).

Chiral Separation of *trans*-2-Propyl-9,10-dimethoxy-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]-phenanthrene (22d). Racemic **22d** was separated on a preparative (50 mm × 500 mm) Chiracel OD column, eluting with a 5% mixture of 2-propanol in hexanes at a flow rate of 50 mL/min, monitoring at 254 nm. Good separation was obtained with samples weighing up to 300 mg. The (−) and (+) enantiomers eluted at 62 and 85 min, respectively (80−85% recovery). **(−)-22d**: $[\alpha]^{25}_D$ = −343° (c = 0.52, methanol); mp 86−87 °C. **(+)-22d**: $[\alpha]_D$ = +335° (c = 1.05, methanol); mp 86−87 °C.

(−)-*trans*-2-Propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol Hydrobromide (5). The title compound was prepared from **(−)-22d** following the procedure described for **12b**: mp 155−62 °C dec; $[\alpha]^{25}_D$ = −167° (c = 1.03, MeOH). Anal. ($C_{18}H_{22}BrNO_2S\cdot 0.7H_2O$) C,H,N.

(+)-*trans*-2-Propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol Hydrobromide (47d). The title compound was prepared from **(+)-22d** following the procedure described for **12b**: $[\alpha]^{25}_D$ = +165° (c = 0.35, ethanol). Anal. ($C_{18}H_{22}BrNO_2S\cdot 0.1HBr$) C,H,N.

The following compounds were prepared from **22b−d** in the same way as described for **5** and **47d**.

(−)-*trans*-2-Ethyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (46b): mp 174−5 °C; $[\alpha]^{25}_D$ = −192.2° (c = 1.01, MeOH). Anal. ($C_{17}H_{20}BrNO_2S\cdot 0.60H_2O$) C,H,N.

(+)-*trans*-2-Ethyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (47b): $[\alpha]^{25}_D$ = +197° (c = 1.02, MeOH). Anal. ($C_{17}H_{20}BrNO_2S\cdot 0.60H_2O$) C,H,N.

(−)-*trans*-2-Methyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (46a): $[\alpha]^{25}_D$ = −162° (c = 1.03, MeOH); mp 201−2 °C. Anal. ($C_{16}H_{18}BrNO_2S\cdot 0.2HBr$) C,H,N.

(+)-*trans*-2-Methyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (47a): $[\alpha]^{25}_D$ = +176° (c = 1.0, MeOH). Anal. ($C_{16}H_{18}BrNO_2S\cdot 0.4HBr$) C,H,N.

(−)-*trans*-2-(1,1-Dimethylethyl)-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (46c): $[\alpha]^{25}_D$ = −193° (c = 1.04, MeOH); mp 167−8 °C. Anal. ($C_{19}H_{24}BrNO_2S\cdot 0.2HBr\cdot 0.2H_2O$) C,H,N.

(+)-*trans*-2-(1,1-Dimethylethyl)-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[*c*]phenanthrene-9,10-diol hydrobromide (47c): $[\alpha]^{25}_D$ = +188° (c = 1.01, MeOH). Anal. ($C_{19}H_{24}BrNO_2S\cdot 0.5H_2O$) C,H,N.

Biological Methods. General. Rat striatal membranes were obtained from Analytical Biological Services (ABS) (Wilmington, DE). The radioligands [^{3}H]SCH 23390, [^{3}H]-spiperone, and [^{3}H]rauwalsine were obtained from DuPont NEN (Boston, MA). [^{125}I]SCH 23982 was obtained from Amersham (Arlington Heights, IL). For the binding assays, the K_i values were determined from the IC_{50} values as described by Cheng and Prussof.[28]

Radioligand Binding Studies: Rat Striatum. Assays were conducted in 96-well microtiter plates using 1 mL minitubes and assay volumes of 250 μL. Rat striatal membranes were resuspended in 50 mM Tris-HCl, 5 mM $MgCl_2$, pH 7.4, at 4 °C. For the D1 binding assay, 10 μg of membrane protein was incubated with [^{125}I]SCH 23982 (0.02 nM, K_d = 1.7 nM), with or without competitor, for 30 min at room temperature. SCH 23390 (1 μM) was used to define nonspecific binding. For the D2 binding assay, 20 μg of membrane protein was incubated with [^{3}H]spiperone (0.5 nM, K_d = 0.08 nM), with or without competitor, at 37 °C for 20 min. (+)-Butaclamol (100 μM) was used to define nonspecific binding. For α2 binding, [^{3}H]rauwaulscine (0.7 nM, K_d = 0.6 nM) was incubated with rat cortical membranes (50 μg of tissue/assay) at room temperature for 60 min. Nonspecific binding was defined with 10 μM phentolamine.

Adenylate Cyclase Activity: Fish Retina. The method for determining cAMP accumulation in fish retina has been described previously.[29] Common Comets, approximately 2−3 in. long, were obtained from Grassy Fork Fisheries (Martinsville, In). Fish were dark-adapted for at least 1 h before sacrificing. Each retina was homogenized in 1.5 mL of ice cold 50 mM Tris-HCl with 0.4 mM EDTA, pH 7.4, at 4 °C. Homogenization procedure, assay buffer, and incubation volume were identical to those described for the rat striatum adenylate cyclase assay. Each retina was used in 100 assay tubes. The incubation was conducted for 10.5 min at 37 °C.

Behavioral Pharmacology. The rat rotation experiments were performed using male Sprague−Dawley rats that were given unilateral lesions of the ascending medial forebrain bundle with 6-OHDA, as described previously.[13b]

The evaluation of the seizuregenic liability of the compounds was carried out using male CD-1 mice (Charles River, Portage, MI) weighing approximately 13−22 g. Clear plastic shoebox cages (28 × 17.5 × 13 cm) containing animal bedding and wire cage lids served as the observation apparatus. Mice were injected subcutaneously with varying doses of test compound or vehicle and immediately placed in the observation cage. Each cage held up to four mice. The animals were observed for behavioral signs of seizure activity that included buccal movements (rhythmic opening and closing of the mouth), forelimb clonus (repetitive rhythmic clawing motion by one or both of the forepaws and may progress to animals adopting

an upright position with arched back and tilted head), clonic seizure, tonic seizure, and death. Bouts of running typically preceded these seizure-like events. From these data, the dose at which at least one-half of the test group animals exhibited seizure-like behaviors (ED_{50}) was calculated.

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