Structure−Activity Studies for a Novel Series of Tricyclic Substituted Hexahydrobenz[*e*]isoindole α_{1A} Adrenoceptor Antagonists as Potential Agents for the Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

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In search of a uroselective agent that exhibits a high level of selectivity for the α_{1A} receptor, a novel series of tricyclic hexahydrobenz[*e*]isoindoles was synthesized. A generic pharmacophoric model was developed requiring the presence of a basic amine core and a fused heterocyclic side chain separated by an alkyl chain. It was shown that the 6-OMe substitution with *R*, *R* stereochemistry of the ring junction of the benz[*e*]isoindole and a two-carbon spacer chain were optimal. In contrast to the highly specific requirements for the benz[*e*]isoindole portion and linker chain, a wide variety of tricyclic fused heterocyclic attachments were tolerated with retention of potency and selectivity. In vitro functional assays for the α_1 adrenoceptor subtypes were used to further characterize these compounds, and in vivo models of vascular vs prostatic tone were used to assess uroselectivity.

Introduction

Benign prostatic hyperplasia (BPH) is a common disease that afflicts middle-aged and elderly males, with the percent incidence of pathological evidence of the disease approximately equal to the man's age.[1] This condition is characterized by a collection of urological symptoms including hesitancy, nocturia, poor urine flow, frequency of urination, and sensations of urgency. While the term BPH suggests that the observed symptoms are due to an increase in organ size causing an obstruction to flow, an important dynamic component to symptomatic BPH has been demonstrated[2] that is mediated primarily through prostatic α_1 adrenoceptors.[3] Clinical efficacy in ameliorating the symptoms of BPH has been shown with several α_1 antagonists, including terazosin,[4] doxazosin,[5] tamsulosin,[6] and alfuzosin.[7] (Chart 1). However, these agents are suboptimal due to the appearance of dose limiting side effects: hypotension, dizziness, muscle fatigue. These side effects are believed to be mediated by the blockade of α_1 receptors in the vasculature and the central nervous system. A highly "uroselective" α_1 adrenoceptor antagonist would therefore represent a major advance in pharmacotherapy for the treatment of BPH.

Within the past decade, the heterogeneity of the α_1 receptor has been realized both on a molecular and pharmacological level.[8] At the molecular level, three subtypes of the human α_1 receptor have been identified and cloned: α_{1a}, α_{1b}, and α_{1d}. These receptors correlate with the pharmacologically defined receptors: α_{1A}, α_{1B}, and α_{1D}. In the human prostate, mRNA for all three subtypes has been found[9] with that for the α_{1a} subtype present in greatest abundance. In addition, the antagonist blockade of norepinephrine- or phenylephrine-induced contractions of human prostate tissue has been found to correlate with affinity for the α_{1a} subtype.[10] In vitro binding selectivity for α_{1a} over α_{1b} has also been shown to correspond with selectivity in vivo for blockade of agonist-induced increases in intraurethral versus arterial pressure.[11] Additional evidence in support of a prominent role for the α_{1B} receptor in the regulation of blood pressure derives from a recent study where α_{1b} knockout mice[12] displayed a substantially reduced responsiveness to phenylephrine-induced increases in blood pressure. The potential role of the α_{1d} receptor in the design of a "uroselective" α_1 antagonist is less clear since the relative contribution of this subtype to the maintenance of prostatic and vascular tone is not well defined. Interestingly, α_{1d} mRNA has been shown to be the dominant α_1 subtype present in the human bladder detrusor.[13] Additional recent evidence suggests that α_{1D} receptor blockade may ameliorate the irritative symptoms of BPH that result from involuntary contractions of the bladder smooth muscle.[14] Thus, a strong scientific rationale exists for the utility of α_1 antagonists selective for α_{1a} over α_{1b}, with activity at α_{1d} potentially providing some additional therapeutic benefit.

The known nonselective α_1 antagonist **1**[15] served as a template for the design of this series. It was reasoned that 9-methoxybenz[*e*]isoindole could serve as a rigidified replacement for the *o*-methoxyphenylpiperazine core of **1**, with the additional conformational restraint possibly resulting improved subtype selectivity (Chart 2). Unfortunately, the initial 9-methoxybenz[*e*]isoindole target **26** exhibited only moderate affinity for the α_{1A} binding site and was nonselective for α_{1A} vs α_{1b}. However, relocation of the OMe substituent from the 9- to the 6-position resulted in compound **18**, posessing both enhanced affinity and improved selectivity for the

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Chart 1

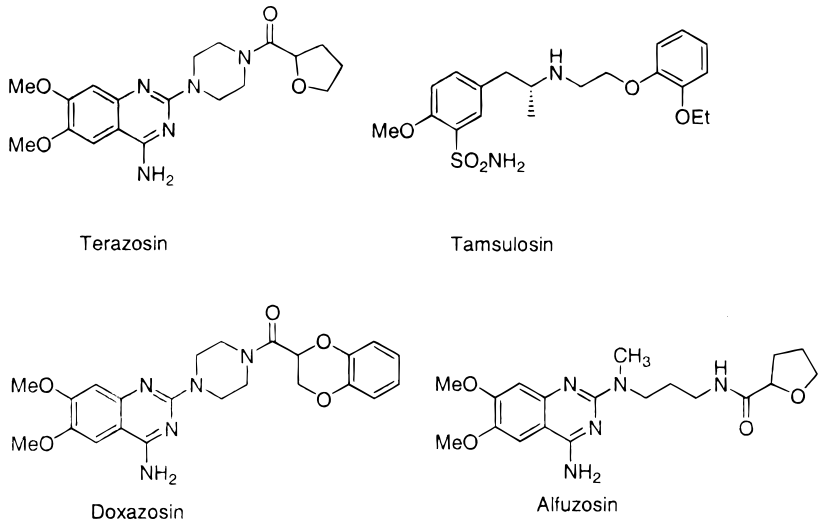
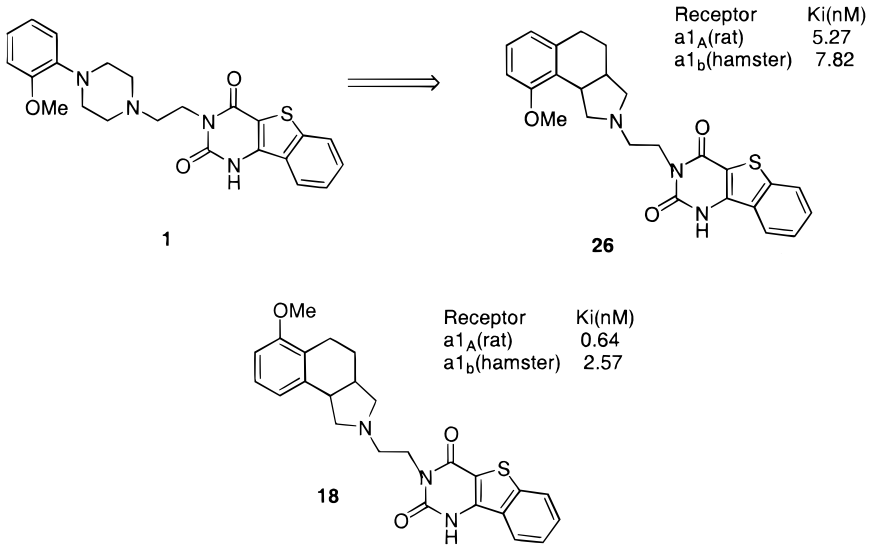


Chart 2



α_{1A} subtype. Encouraged by these results, an extensive SAR study was initiated based on the 6-methoxybenz[*e*]isoindole core.

Chemistry

SAR studies of the parent structure involved investigation of variously substituted benz[*e*]isoindoles, identification of the optimal stereochemistry of the ring junction, optimization of the tether length, and studies of the various replacements of the tricyclic heterocyclic attachment of the molecule (Figure 1). Target compounds were synthesized by one of two general methods (Scheme 1), and the two methods are exemplified by the synthesis of the benzothienopyrimidinediones **18**−**20**. In method A, the aminoesters **16** were reacted with 2-chloroethyl isocyanate[15] to yield the haloalkyl ureas **17** that were in turn reacted with the benz[*e*]isoindoles **6** (see Scheme 2) to yield the final products. In method B, the heterocycle was prepared for coupling by reaction of the aminoester **16** with triphosgene to yield the isocyanate, which was in turn reacted with the aminoethylbenz[*e*]isoindole **7** to yield an intermediate urea. This urea cyclized either spontaneously or upon treatment with base (KOtBu in THF) to produce the pyrimidinedione final product.

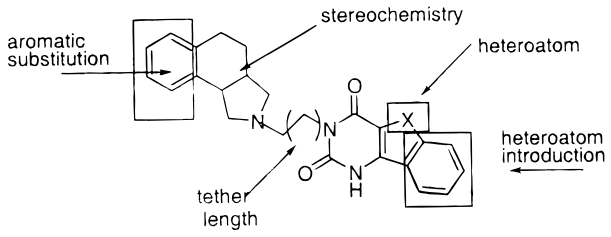
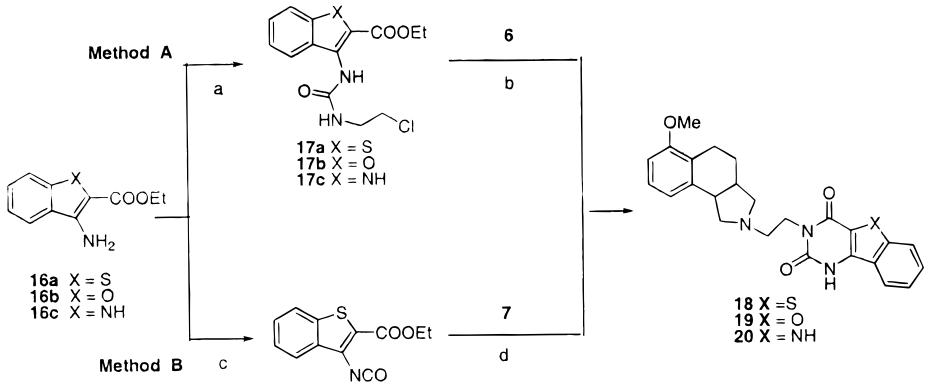


Figure 1. SAR of compound **18**.

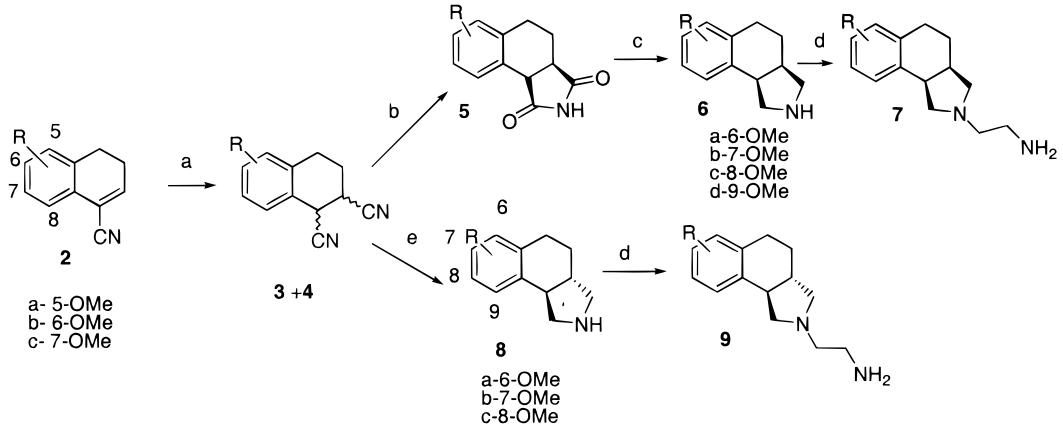
The starting racemic *cis*-benz[*e*]isoindoles **6** were prepared from the corresponding dihydronaphthalene-1-carbonitriles **2**[16] in several steps (Scheme 2). Addition of LiCN to nitriles **2** afforded a mixture of *cis* **3** and *trans* **4** dinitriles. The mixture could be easily separated by column chromatography on silica gel eluting with hexane:ethyl acetate. Cyclization of the dinitrile intermediates **3** to the cyclic imides **5** by the action of HBr, followed by reduction with diborane in THF, yielded the desired racemic *cis* benz[*e*]isoindoles **6**. When *trans* dinitrile **4** was subjected to similar HBr treatment, the

Scheme 1[a]



[a] Conditions and reagents: (a) 2-chloroethyl isocyanate; (b) DMSO, diisopropylethylamine; (c) phosgene, Et_3N; (d) (i) CH_2Cl_2, rt, (ii) KOtBu.

Scheme 2[a]



[a] Conditions and reagents: (a) LiCN/DMF, separate by flash chromatography; (b) HBr/DMF; (c) BH_3/THF; (d) (i) $ClCH_2CN$, ethyldiisopropylamine, (ii) $LiAlH_4$; (e) H_2/Raney Ni, NH_4OH.

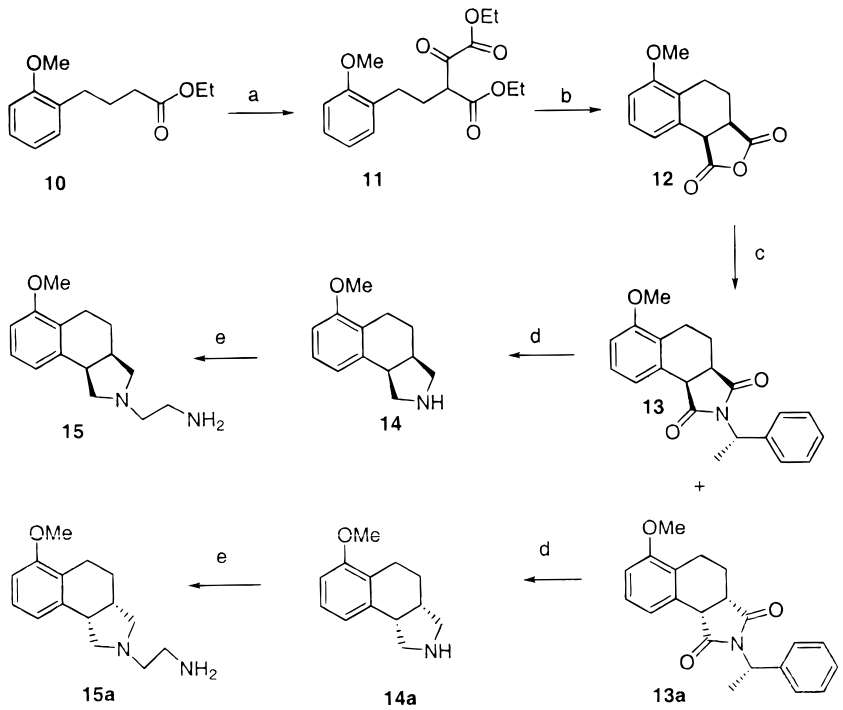
reaction proceeded sluggishly and the resulting product was *cis* benz[*e*]isoindole **6**. Consequently the conversion of dinitriles to *cis* benz[*e*]isoindoles **6** can be done without prior separation of diastereomers. The synthesis of *trans* benz[*e*]isoindoles **8** was achieved by the catalytic hydrogenation of the dinitriles **4** with Raney Ni in the presence of methanolic ammonia. These conditions facilitated the predominant formation of *trans* benz[*e*]-isoindoles (10:1). Interestingly, treatment of the *cis* dinitriles **3** under these hydrogenation conditions also provided the predominant formation of the *trans* benz-[*e*]isoindoles(10:1).[35] *cis*- 9-Methoxybenz[*e*]isoindole **6d** was prepared from 5-bromo-8-methoxydihydronaphthalene carbonitrile.[17]

Aminoalkylbenz[*e*]isoindoles **7** and **9** (Scheme 2) were synthesized via alkylation of the benz[*e*]isoindoles **6** and **8** with chloroacetonitrile followed by reduction of the nitrile with either lithium aluminum hydride or alane. Lengthening of the tether was accomplished when 3-chloropropionitrile was used instead of chloroacetonitrile in the synthesis of primary amines. For the four-carbon chain an alternative method was utilized. 5-Methoxy-1,2,3,4-tetrahydronaphthalene-*cis*-1,2-dicarboxylic acid diethyl ester[18] was reduced with lithium aluminum hydride to the corresponding diol, which in turn was converted to the corresponding bis-mesylate. The desired 4-aminobutylbenz[*e*]isoindole was synthesized by the reaction of the mesylate with 1,4-diaminobutane.

The preparation of single enantiomers of *cis* 6-methoxybenz[*e*]isoindole is shown in Scheme 3. Base promoted condensation of the ester **10**[19] with diethyl oxalate yielded the keto diester **11**, which was converted to **12** by cyclization with sulfuric acid and subsequent catalytic hydrogenation. Dehydrative condensation of the anhydride with (*S*)-α-methylbenzylamine yielded a diastereomeric mixture of imides. The (3a*R*,9b*R*) imide **13** was separated by crystallization and reduced with diborane to give the *N*-benzyl substituted pyrrolidine. Catalytic hydrogenation afforded the resolved (3a*R*,9b*R*)-6-methoxy-benz[*e*] isoindole **14**. Alkylation with chloroacetonitrile and reduction with $LiAlH_4$ gave the primary amine **15**. The (3a*S*,9b*S*) imide **13a** was obtained from the filtrate of the aforementioned crystallization and treated similarly to yield the primary amine **15a**.

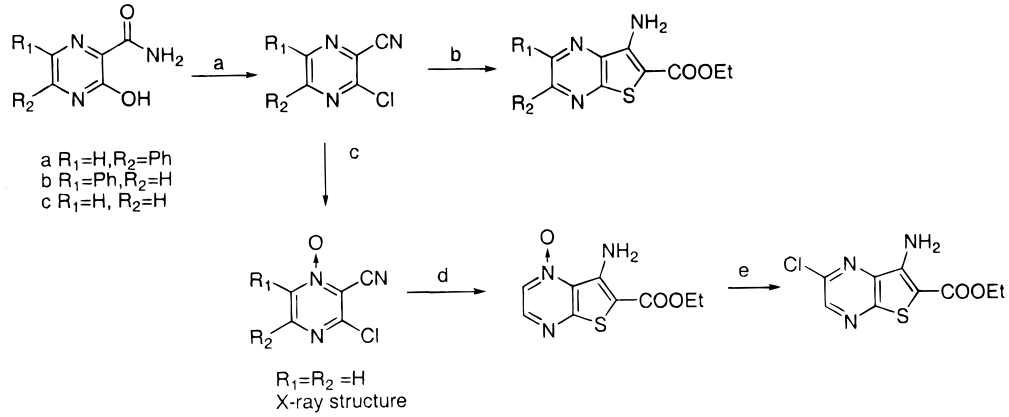
Pyrazinothiophenes used in this study were prepared from the corresponding chloropyrazinonitriles and ethylthioglycolate (Scheme 4). In order to obtain chloro and methoxy-substituted pyrazinothiophene derivatives, chloropyrazinonitriles were first oxidized to the corresponding *N*-oxides. X-ray studies established the position of oxidation. The obtained pyrazine *N*-oxides were converted to pyrazinothiophenes by treatment with ethylthioglycolate in the presence of base and then subjected to chlorination with phosphorus oxychloride. The various substituted benzothiophenes were synthesized by the same methodology from the corresponding chlo-

Scheme 3[a]



[a] Conditions and reagents: (a) KOtBu, diethyl oxalate; (b) (i) H_2SO_4, (ii) H_2, Pd; (c) (*S*)-α-methylbenzylamine; (d) (i) BH_3·THF, (ii) H_2, Pd; (e) (i) $ClCH_2CN$, ethyldiisopropylamine, (ii) $LiAlH_4$.

Scheme 4[a]



[a] Conditions and reagents: (a) $POCl_3/Et_3N$; (b) ethylthioglycolate, Na_2CO_3; (c) $K_2S_2O_8/H_2SO_4$; (d) ethylthioglycolate, Na_2CO_3; (e) $POCl_3$.

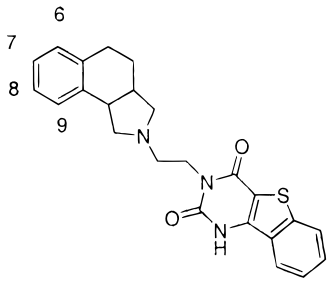
robenzonitriles or nitrobenzonitriles.[20] The synthesis of pyridothiophenes from the corresponding chloropyridonitriles and methylthioglycolate was described by Dunn.[21]

Results and Discussion

Target compounds were evaluated for their affinity at the α_{1A}, α_{1b}, and α_{1d} receptors. The structural features evaluated in the study are summarized in Chart 1, and include: (i) optimization of the aromatic substitution and stereochemistry of the ring fusion of the benz[*e*]-isoindole portion of the molecule, (ii) length of the tether, (iii) heteroatom substitutions in the center ring of the pyrimidinedione substructure, and (iv) introduction of heteroatoms into the aromatic ring of the pyrimidinedione substructure.

Two aspects of the SAR of the benz[*e*]isoindole nucleus were explored: aromatic substitution with OMe, and ring fusion stereochemistry (Table 1). Although 9-OMe substitution appears to most closely mimic the *o*-methoxyphenylpiperazine substructure, this substitution was not optimal for the benz[*e*]isoindole. The 9-methoxybenz[*e*]isoindole analogue **26** did not display selectivity for the α_1 receptors and exhibited only moderate affinity for the α_{1A} subtype. The 6-methoxy analogue **18** exhibited improved selectivity and increased affinity for the α_{1A} receptor and was the optimal position for substitution on this ring system. Methoxy substitution in the 7- and 8-positions was deleterious to affinity. Exploration of the relative and absolute stereochemistry of the benz[*e*]isoindole ring fusion revealed that the relative stereochemistry (*cis* vs *trans*) did not have a significant impact on either selectivity or potency for the α_1 subtypes. However, the 3a*R*,9b*R* *cis*-enantiomer **22** was 20-fold more active than the antipode **23**, indicating a clear preference for the *R*,*R* absolute stereochemistry. Table 2 examines the effect of the spacer chain length on the activity. Among a

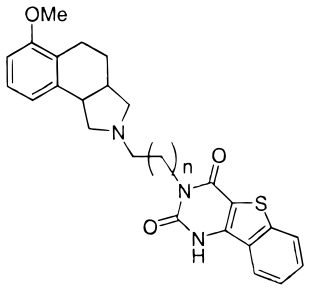
Table 1. Effect of Benz[*e*]isoindole Stereochemistry and Substitution on Selectivity



no.	R	stereochemistry	radioligand binding K_i (nM) α_{1A}[a]	α_{1b}[a]	α_{1d}[a]	selectivity ratio[b]
terazosin			0.82 (0.60, 1.12)	0.69 (0.59, 0.80)	1.01 (0.06, 0.07)	0.84
tamsulosin			0.03 (0.025, 0.032)	0.20 (0.18, 0.23)	0.07 (0.068, 0.073)	7.0
18	6-OMe	rac (*cis*)	0.64 (0.56, 0.73)	2.57 (2.07, 3.19)	0.37 (0.32, 0.43)	4.0
21	6-OMe	rac (*trans*)	1.08 (0.91,1.29)	3.43 (3.19, 3.69)	0.63 (0.55, 0.74)	3.17
22	6-OMe	*R,R*	0.47 (0.38, 0.58)	2.62 (2.35, 2.93)	0.94 (0.62, 1.44)	5.57
23	6-OMe	*S,S*	9.03 (8.70, 9.21)	14.01 (13.11, 14.97)	6.28 (5.43, 7.21)	1.55
24	7-OMe	rac (*cis*)	38.1 (30.6, 47.4)	119 (104, 138)	47 (47, 37)	3.12
25	8-OMe	rac (*cis*)	12.8 (11.6, 14.2)	37.9 (32.5, 44.3)	5.76 (4.15, 7.98)	2.95
26	9-OMe	rac (*cis*)	5.27 (4.48, 6.2)	7.82 (6.77, 9.04)	8.67 (5.29, 14.21)	1.48

[a] Number of determinations ≥ 3.Values in parentheses are the upper and lower limits derived as a result of the SEM. [b] Selectivity ratio = $K_i(\alpha_{1b})/K_i(\alpha_{1A})$.

Table 2. Effects of Tether Length on Selectivity



no.	*n*	stereochemistry	radioligand binding K_i (nM) α_{1A}[a]	α_{1b}[a]	α_{1d}[a]	selectivity ratio[b]
18	1	rac (*cis*)	0.64 (0.56, 0.73)	2.57 (2.1, 3.2)	0.37 (0.32, 0.43)	4.01
27	2	rac (*cis*)	17.1 (15.1, 19.2)	14.5 (13.7, 15.2)	7.7 (5.4, 11.1)	0.85
28	3	rac (*cis*)	7.43[c]	9.95[c]	4.77[c]	1.33

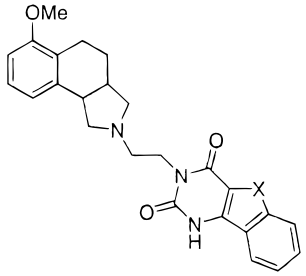
[a] Number of determinations ≥ 3. Values in parentheses are the upper and lower limits derived as a result of the SEM. [b] Selectivity ratio = $K_i(\alpha_{1b})/K_i(\alpha_{1A})$. [c] Number of determinations = 1.

series of 6-OMe substituted benz[*e*]isoindole analogues, the two-carbon linker was clearly preferred.

On the basis of these preliminary findings, an extensive SAR study of the attached heterocycle was initiated. Although only minor differences were observed upon alteration of the center ring heterocycle (see Table 3), the thiophene substructure was selected for the remainder of the SAR study based principally on ease of synthesis. Substitution on the phenyl ring of the benzothiophene substructure was studied extensively (Table 4) but, in most cases, failed to produce compounds of significantly greater potency and selectivity than the parent compound 18, with the exception of compounds **29** and **37** that showed >10-fold selectivity. Certain substitutions were, however, poorly tolerated. Introduction of substituents in the 6-position as in **43** and **44** was clearly detrimental for affinity.

Whereas phenyl ring substitution was not a particularly useful approach, replacement of the phenyl ring with various nitrogen-containing heterocycles resulted in numerous compounds exhibiting significantly improved α_{1A} selectivity. Table 5 summarizes the results

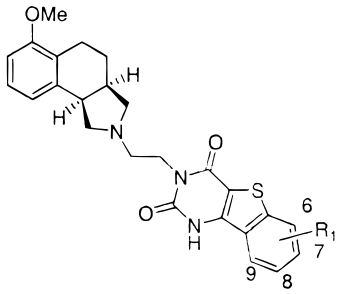
Table 3. Effect of the Heteroatom Replacement



no.	X	stereochemistry	radioligand binding K_i (nM) α_{1A}[a]	α_{1b}[a]	α_{1d}[a]	selectivity ratio[b]
18	S	rac (*cis*)	0.64 (0.56, 0.73)	2.57 (2.1, 3.2)	0.37 (0.32, 0.43)	4.01
19	O	rac (*cis*)	2.17 (1.81, 2.60)	5.39 (4.98, 5.84)	0.68 (0.61, 0.76)	2.48
20	NH	rac (*cis*)	0.79 (0.57, 1.11)	2.25 (2.11, 2.41)	0.74 (0.57, 0.96)	2.52

[a] Number of determinations ≥ 3. Values in parentheses are the upper and lower limits derived as a result of the SEM. [b] Selectivity ratio = $K_i(\alpha_{1b})/K_i(\alpha_{1A})$.

Table 4. Effect of Phenyl Ring Substitution

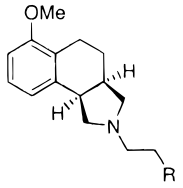


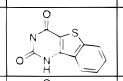
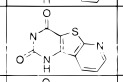
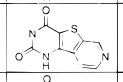
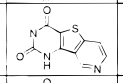
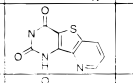
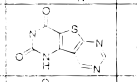
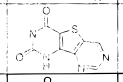
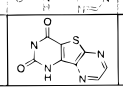
no.	R_1	radioligand binding K_i (nM) α_{1A}[a]	α_{1b}[a]	α_{1d}[a]	selectivity ratio[d]
18		0.64 (0.56, 0.73)	2.57 (2.1, 3.2)	0.37 (0.32, 0.43)	4.01
29	7-CN	0.40 (0.26, 0.61)	6.20 (5.39, 7.14)	0.74 (0.57, 0.96)	15.5
30	7-$CONH_2$	0.29 (0.20, 0.43)	0.86 (0.56, 1.30)	0.27 (0.20, 0.37)	2.9
31	7-CF3	9.27[c]	23.8[c]	6.84[c]	2.56
32	8-CN	1.64 (1.14, 2.36)	14.3 (11.2, 18.2)	0.59 (0.40, 0.88)	8.7
33	8-COOMe	4.75[c]	14.3[c]	2.84[c]	3.01
34	8-$CON(Me)_2$	0.28[c]	1.7[c]	0.63[c]	6.07
35	8-NO_2	1.28[b] (1.21, 1.37)	8.49[b] (8.29, 8.70)	1.31[b] (0.90, 1.91)	6.64
36	8-Me	2.16[c]	4.26[c]	1.04[c]	1.97
37	8-$CONH_2$	0.52 (0.46, 0.60)	6.34 (4.62, 8.7)	0.51 (0.42, 0.62)	12.2
38	8-Cl	0.44[b] (0.45, 0.45)	1.91[b] (1.61, 2.27)	0.31[b] (0.24, 0.38)	4.34
39	9-Cl	0.51[c]	3.15[c]	1.32[c]	6.17
40	9-OMe	0.77[c]	3.1[c]	1.07[c]	4.0
41	9-CN	3.3[c]	35.8[c]	6.6[c]	10.8
42	9-Me	1.29[c]	6.95[c]	0.88[c]	5.38
43	6-Cl	98.9[b] (49.4, 198)	1220[b] (148.8, 10000)	25[b] (14.1, 44.5)	12.3
44	6-CN	6.35[c]	26.9[c]	2.08[c]	4.24

[a] Number of determinations ≥ 3. Values in parentheses are the upper and lower limits derived as a result of the SEM. [b] Number of determinations = 2. [c] Number of determinations = 1. [d] Selectivity ratio = $K_i(\alpha_{1b})/K_i(\alpha_{1A})$.

of the phenyl ring replacement with various heterocycles. The four isomeric pyridine analogues **45**−**48** showed an incremental improvement in selectivity for the α_{1A} receptor. The pyrimidine analogue **49** and the pyrazine analogue **51** displayed a further enhancement in selectivity with retention of sub-nanomolar affinity for the α_{1A}binding site. Further SAR studies explored the effect of substituents on the heterocyclic ring (Table 6). The greatest selectivity (α_{1A} vs α_{1b}) was achieved with the substituted pyrazine analogues (**57**, **58**, and

Table 5. Effect of Heterocycle Replacement



#	R	Radioligand Binding K_i (nM)* α_{1A}[a]	α_{1b}[a]	α_{1d}[a]	Selectivity ratio[c]
22		0.47 (0.38, 0.58)	2.62 (2.35, 2.93)	0.94 (0.62, 1.44)	5.57
45		0.59 (0.53, 0.66)	6.12 (5.51, 6.79)	0.69 (0.61, 0.79)	10.4
46		0.53 (0.47, 0.61)	3.33 (2.96, 3.74)	0.37 (0.27, 0.50)	6.28
47		0.33 (0.30, 0.36)	4.63 (4.19, 5.12)	0.28 (0.24, 0.32)	14
48		0.27 (0.22, 0.35)	3.39 (3.05, 3.77)	0.51 (0.41, 0.64)	12.5
49		0.68 (0.64, 0.72)	15.5 (13.9, 17.1)	2.08 (1.90, 2.27)	22.8
50		1.62[b] (1.55, 1.69)	15.9[b] (12.7, 19.8)	3.74[b] (3.27, 4.27)	9.8
51		0.72 (0.54, 0.96)	12.5 (11.5, 13.6)	2.06 (2.02, 2.09)	17.3

[a] Number of determinations ≥ 3. Values in parentheses are the upper and lower limits derived as a result of the SEM. [b] Number of determinations = 2. [c] Selectivity ratio = $K_i(\alpha_{1b})/K_i(\alpha_{1A})$.

60). Although a phenyl ring is relatively well tolerated in the R_2-position (**58**), introduction of a phenyl group in the R_1-position (59) led to a dramatic loss of receptor binding affinity.

Functional assays for pharmacologically defined α_1 adrenoceptors were used to further characterize the most selective compounds. Receptors were classified using phenylephrine (PE) challenge in dog prostate (α_{1A}),[22] rat vas deferens (α_{1A}),[23] and rat spleen (α_{1B}).[23] For each of these models, agonist dose−response curves were repeated against increasing concentrations of test antagonist, and Schild plot analysis was used to determine the pA2 value (Table 7). With the exception of tamsulosin, functional antagonist selectivity was highly correlated to receptor subtype binding affinity. Nonselective α_1 antagonists such as terazosin (as defined by receptor binding affinity) also failed to demonstrate functional antagonist selectivity, whereas the most selective compounds from this study (i.e., 60) based on receptor binding affinity also exhibited the greatest selectivity in in vitro functional models.

This same set of the most α_{1A} selective compounds was further evaluated in two in vivo models: an intraurethral pressure (IUP) model as a measure of efficacy and the spontaneously hypertensive rat (SHR) model as a measure of hypotensive liability. The IUP model used aged male anesthesized dogs, in which a pressure transducer was inserted through the urethra to the region of prostate. Phenylephrine caused a dose related increase in intraurethral pressure which was blockable by α_{1A} antagonists. Dose−response curves were generated at varying antagonist doses. From these data a pseudo pA2 value could be generated to calculate the dose required to produce a 2-fold rightward shift of the agonist dose−response curve. Hypotensive activity of test compounds was assesed in the (SHR) model using an ascending iv dosing paradigm and measuring the decrease in blood pressure averaged over a 60 min period. From the area under the curve (T_{60} AUC) an ED_{50} value was calculated as the dose required to produce a decrease in mean arterial pressure equivalent to 50% of normotensive. Measuring the blood pressure over only a 60 min period was chosen to minimize the potential imput on variable pharmacokinetics between compounds. Pseudo pA2 values from the IUP model and pED_{50} values from the SHR model are reported in Table 8. Although the absolute selectivity ratios determined in vivo are an order of magnitude greater than the in vitro selectivity ratios, the rank order selectivity across this series of α_1 antagonists is nearly identical (terazosin ≈ doxazosin ≈ alfuzosin < tamsulosin < **22** ≈ **45** ≈ **48** < **60**). The high correlation between receptor affinity to subtypes of the α_1 receptor, functional response in target tissues, and the in vivo response to relax prostatic smooth muscle vs blood pressure control adds further evidence to support the hypothesis that the α_{1A} subtype differentially mediates prostatic tone and the α_{1B} subtype mediates vascular tone.

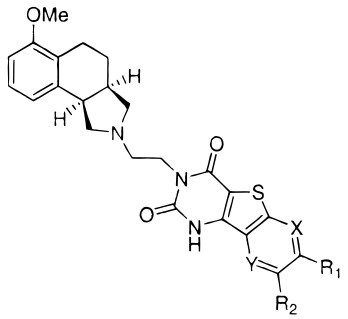
Conclusion

A structurally novel series of α_1-antagonists, possessing a benz[*e*]isoindole unit attached to a pyrimidinedione heterocycle via an alkyl chain, was described. 6-Methoxy substitution on the benz[*e*]isoindole portion, *R*,*R* stereochemistry, and a two-carbon linker were found to be optimal for α_1 activity. A variety of heterocyclic attachments to this core were found that display high affinity for the α_{1A} adrenoceptor and >10-fold selectivity over the α_{1b} subtype. Compound **60** showed the highest degree of selectivity in the radioligand binding assays (50-fold), in the in vitro functional assays (40-fold), and for in vivo prostate selectivity (3200-fold). This correlation is further evidence that prostatic smooth muscle tone is primarily mediated by the α_{1A} subtype. A number of the compounds in this study with >10-fold selectivity for α_{1A} over α_{1b} also possess appreciable affinity for the α_{1d} subtype. Given the possible influence of the α_{1D} receptor on the irritative symptoms of BPH, this is an extremely attractive profile for a clinical agent. Thus, compounds such as **60** have the potential to not only improve the objective symptoms of BPH such as urinary flow rate through selectivity for α_{1A} over α_{1B}, but to also alleviate the subjective symptoms by antagonism of the α_{1D} receptor at the level of the bladder smooth muscle.

Experimental Section

Biology. Radioligand Binding Assays. The compounds were evaluated for α_1 adrenoceptor binding affinity in vitro using [^{3}H]-prazosin as the radioligand, two cloned α_1 adrenoceptors expressed in LTK cell: (α_{1b} (hamster), and α_{1d} (rat)) and the pharmacologically defined α_{1A} adrenoceptor (rat submaxillary gland). Radioligand binding assays were performed as described previously by Knepper et al.[24] Briefly, recombinant α_1-adrenoceptors were stably expressed in mouse fibroblast cells (LTK$^-$) grown in roller bottle cultures to provide

Table 6. SAR of Pyrazine and Pyridine Substitution



no.	X	Y	R1	R2	radioligand binding K_i (nM) α_{1A}[a]	α_{1b}[a]	α_{1d}[a]	selectivity ratio[c]
52	CH	N	H	Cl	0.38 (0.30, 0.48)	4.15 (3.03, 5.67)	0.61 (0.46, 0.79)	11
53	CH	N	H	OMe	0.66 (0.50, 0.88)	3.0 (1.99, 4.50)	1.1 (0.7, 1.7)	4.5
54	C-Cl	N	H	H	3.13 (2.37, 4.14)	61.6 (42.5, 89.3)	4.16 (3.4, 5.1)	19.7
55	C-OMe	N	H	H	0.79 (0.73, 0.87)	6.69 (5.54, 8.08)	1.41 (1.16, 1.72)	8.45
56	N	N	Me	H	0.49 (0.42, 0.58)	13.5 (11.4, 15.9)	2.31 (1.97, 2.7)	27.5
57	N	N	Me	Me	0.39 (0.38, 0.40)	13.9 (13.7, 14.1)	3.28 (2.73, 3.92)	35.6
58	N	N	H	Ph	3.91 (3.14, 4.87)	120 (90, 160)	19.8 (17.7, 22.1)	30.7
59	N	N	Ph	H	153[b] (125, 187)	1853[b] (343, 10000)	160[b] (125, 205)	12
60	N	N	H	Cl	0.69 (0.50, 0.98)	35.1 (24.5, 50.3)	3.83 (3.11, 4.71)	50.9
61	N	N	H	OMe	0.35 (0.35, 0.37)	3.73 (3.41, 4.07)	1.10 (0.99, 1.21)	10.6

[a] Number of determinations ≥ 3. Values in parentheses are the upper and lower limits derived as a result of the SEM. [b] Number of determinations = 2. [c] Selectivity ratio = $K_i(\alpha_{1b})/K_i(\alpha_{1A})$.

Table 7. In Vitro Profile of Benz[*e*]isoindole Antagonists in Comparison with Other Adrenergic Antagonists

antagonist	pA2[a] rat vas deferens	pA2[a] rat spleen	pA2[a] dog prostate	selectivity ratio[b]
terazosin	8.04 ± 0.45	8.6 ± 0.46	7.44 ± 0.24	0.27
doxazosin	8.69 ± 0.70	9.51 ± 0.41	7.59 ± 0.20	0.15
alfuzosin	7.61 ± 0.13	8.31 ± 0.12	6.66 ± 0.10	0.20
tamsulosin	9.47 ± 0.21	9.69 ± 0.44	9.54 ± 90.17	0.60
22	8.71 ± 0.45	7.59 ± 0.12	8.63 ± 0.34	13
45	8.65 ± 0.15	7.79 ± 0.15	8.78 ± 0.32	7.4
48	8.93 ± 0.18	7.89 ± 0.22	9.11 ± 0.15	10.9
60	8.96 ± 1.06	7.35 ± 0.64	9.35 ± 0.82	41

[a] Data expressed as $pA_2 \pm$ SEM; slopes are not different from unity. Number of determinations ≥ 3. [b] Selectivity ratio = antilog[pA2(rat v.d./pA_2(rat.s.)].

Table 8. Comparison of Antagonists in the IUP and SHR Models.

antagonist	IUP (pseudo pA2)[a] (95% C. L.)	SHR (pseudo pED_{50})[a] (±SEM)	selectivity ratio[b]
terazosin	7.02 (6.36−7.69)	6.64 ± 0.76	2.4
doxazosin	7.12 (6.54−7.70)	6.50 ± 0.63	4.2
alfuzosin	6.87 (6.46−7.28)	6.58 ± 0.62	1.9
tamsulosin	8.87 (8.41−9.33)	7.33 ± 0.30	35
22	7.73 (7.33−8.13)	5.0 ± 0.17	537
45	8.25 (7.80−8.45)	5.35 ± 0.11	589
48	8.17 (7.60−8.74)	5.33 ± 0.74	690
60	8.28 (7.84−8.72)	4.77 ± 0.19	3236

[a] Number of determinations ≥ 3. [b] Selectivity ratio = antilog(pA2−pED_{50}).

cell membranes for subsequent receptor binding characterization studies. Membranes were prepared from confluent cells, and aliquots of the pooled homogenates were frozen in N_2(l) and stored at −70 °C until the time of assay. Radioligand binding was performed as follows: tubes containing 0.05 mL of water (total binding), 0.05 mL of 10−5 M final concentration of phentolamine (nonspecific binding) or 0.05 mL of compound of interest, 0.45 mL of [^{3}H]-prazosin, approximately 200 pM, and 0.5 mL of receptor preparation (generally 0.83 mg wet weight or approximately 0.1 mg of protein per assay tube) in 50 mM Tris-HCl (pH = 7.4) and samples were incubated for 60 min at 25 °C. All assays were terminated by filtration under vacuum through Whatman GF/B filters. Data were analyzed as previously described.[24]

In Vivo Models. Determination of Intraurethral Pressure (IUP) in Dogs. Beagle dogs (Marshall Farms, North Rose, NY) greater than 2 years of age and weighing between 12 and 15 kg were preanesthetized with thiophenal sodium 15 mg/kg iv and then anesthetized using isoflurane. A 7F balloon catheter (Multiflex-list no. 41224-01, Abbott) was inserted into the urethral orifice until the balloon tip was placed well inside the bladder. The balloon was then inflated with 1 mL of room air and the catheter slowly withdrawn just past the first resistance that is felt at the bladder neck. The balloon port of the catheter was connected to a Gould Statham P23Dd pressure transducer interfaced to a computerized data acquisition system (Modular Instruments, Inc) for the measurement of IUP. Dogs were then treated with propranolol (100 μg/kg iv) to block the β-adrenoceptor agonist effect of epinephrine. Dose−response curves of the intraurethral pressor effect of epinephrine were obtained before and after each dose of a test antagonist. The estimated antagonist dissociation constant (in vivo pseudo pA2) was determined by Schild analysis.[25]

Spontaneously Hypertensive Rat (SHR) Model. Male spontaneously hypertensive rats (300−325 g) were briefly anesthetized with Penthrane and the left femoral artery and

vein catheterized for the measurement of mean arterial pressure (MAP) and drug administration, respectively. After a 2.5 h recovery period, the arterial catheter was connected to a Gould Statham p23ID transducer and the pressure waveform was recorded. Mean arterial pressure (MAP, mmHg) and heart rate (HR, beats/min) were determined online using a BUXCO cardiovascular analyzer. After a 30 min predose control period each rat was given one dose of a test antagonist iv, and the MAP and HR were measured over a 60 min period. The area under the hypotensive dose−response curve(T_{60} AUC) was determined using a trapezoidal rule integration of the percent change from the control arterial pressure data set. The antagonist T_{60} AUC was compared to that of a hypothetical antagonist producing complete normalization of blood pressure for 60 min. The ED_{50} value was determined as the dose required to produce a T_{60} AUC equivalent to a 50% change to normotensive.

Chemistry. Proton NMR spectra were obtained on a General Electric QE 300 or QZ 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories. Column chromatography was carried out on silica gel 60 (230−400 mesh). Thin-layer chromatography (TLC) was performed using 250 mm silica gel 60 glass-backed plates with F254 as indicator. Optical rotations were measured with a Perkin-Elmer 541 polarimeter. All physical data and yields for final compounds correspond to the indicated salt form unless otherwise noted.

***trans* and *cis*-5-Methoxy-1,2,3,4-tetrahydronaphthalene-1,2-dinitrile (3a and 4a).** Acetic acid (1.80 mL, 31.5 mmol) was added to a 0.5 M solution of LiCN in DMF (72 mL, 36 mmol). The solution was cooled to 5 °C, and 5-methoxy-3,4-dihydronaphthalene-1-carbonitrile **2**[16] was added (5.55 g, 30 mmol). The cooling bath was removed, and the reaction was allowed to stir at room temperature for 15 min. The reaction was quenched by the addition of H_2O (200 mL) and extracted with Et_2O (2 × 150 mL). The combined organic extracts were washed with H_2O (2 × 150 mL), 5% $NaHCO_3$ (150 mL), and brine (150 mL), dried ($MgSO_4$), and evaporated in vacuo to yield 6.17 g (97%) of a mixture of **3a** and **4a**. The isomers were separated by chromatography on silica gel (3:1 hexane: EtOAc) to yield 2.35 g (37%) of the *trans* isomer **4a**, mp 122−3 °C, as the less polar diastereomer. ^{1}H NMR ($CDCl_3$) δ 2.2 (m, 1H), 2.4 (m, 1H), 2.9 (m, 2H), 3.3 (ddd, 1H, J = 4, 7, and 8 Hz), 3.8 (s, 3H), 4.2 (d, 1H, J = 7 Hz), 6.8 (d, 1H, J = 8 Hz), 7.0 (d, 1H, J = 8 Hz), 7.3 (t, 1H, J = 8 Hz). MS (DCI/NH_3) *m/e* 230 $(M + H)^+$. Anal. ($C_{13}H_{12}N_2O$) C, H, N.

Further elution yielded 3.11 g (49%) of the *cis* isomer **3a** as the more polar diastereomer, mp 110−12 °C. ^{1}H NMR ($CDCl_3$) δ 2.3 (m, 2H), 2.7 (m, 1H), 3.0 (m, 1H), 3.2 (ddd, 1H, J = 4, 5, and 9 Hz), 3.8 (s, 3H), 4.8 (d, 1H, J = 5 Hz), 6.8 (d, 1H, J = 8 Hz), 7.0 (d, 1H, J = 8 Hz), 7.3 (t, 1H, J = 8 Hz). MS (DCI/NH_3) *m/e* 230 $(M + H)^+$. Anal. ($C_{13}H_{12}N_2O$) C, H, N.

***cis*-6-Methoxy-3a,4,5,9b-tetrahydro-1*H*-benz[*e*]isoindole 1,3-(2*H*)-dione (5a).** A solution of the dinitrile **3a** (5.13 g, 22.3 mmol) in CH_2Cl_2 was cooled to 0 °C as HBr (gas) was bubbled through for 2 h. The solution was stirred at 0 °C for an additional hour. The solvent was removed in vacuo to yield an orange glass which was dried briefly (in vacuo), then a N_2 purged solution of 50 mL of water/25 mL of DMF was added. The black solution was heated on the steam bath for 2 h and was allowed to stand overnight at room temperature. The precipitate was filtered, washed with cold water/EtOH (75 mL/25 mL), then dried to yield **5a** (2.89 g, 55%).^{1}H NMR (DMSO-d_6) 1.62 (m, 1H), 2.08 (m, 2H), 2.82 (m, 1H), 3.3 (m, 1H), 3.78 (s, 3H), 4.09 (d, 1H), 6.86 (d, 1H), 7.04 (d, 1H), 7.19 (t, 1H), 11.25 (bs, 1H). MS (DCI/NH_3) *m/e* 232 $(M + H)^+$.

***cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]isoindole Hydrochloride (6a).** To a solution of the imide **5a** (0.89 g, 3.8 mmol) in THF (10 mL), cooled to 0 °C, was added 1 M BH_3 in THF (30.4 mL). The reaction mixture was stirred at reflux for 2 h and then was cooled to 0 °C. Excess methanolic HCl was added dropwise. The mixture was stirred at reflux for 0.5 h, then solvents were evaporated, and water was added. The water solution was extracted with CH_2Cl_2 (2×), and the extracts were set aside. The water layer was basified with 1 M KOH solution and extracted with CH_2Cl_2 (2×). The combined basic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated to yield a yellow oil (0.69 g, 79%). The free base was converted to the HCl salt **6a**, mp 217−18 °C. ^{1}H NMR ($CDCl_3$) (free base) δ 1.51 (m, 1H), 1.80 (m, 1H), 1.90 (s, 1H), 2.50 (m, 2H), 2.78 (m, 3H), 3.21 (q, 1H), 3.32 (dd, 1H, J = 8,11 Hz), 3.42 (dd, 1H, J = 7,11 Hz), 3.81 (s, 3H), 6.70 (d, 1H, J = 8 Hz), 6.78 (d, 1H, J = 8 Hz), 7.12 (t, 1H, J = 8 Hz). MS (DCI/NH_3) *m/e* 204 $(M + H)^+$, 221 $(M + NH_4)^+$. Anal. ($C_{13}H_{18}ClNO$) C, H, N.

***trans*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]isoindole Hydrochloride (8a).** The dinitrile **4a** (1.00 g)was dissolved in 24 mL MeOH and 2 mL anhydrous NH_3. Raney Ni (#28, 3.0 g) was added, and the reaction was shaken under 4 atm of H_2 pressure at 25 °C for 48 h. The reaction was then filtered and evaporated to dryness, and the resulting product was purified by column chromatography (95:4:1 CH_2Cl_2: methanol:Et_2NH) to yield **8a**, mp >260 °C. ^{1}H NMR ($CDCl_3$) (free base) δ 1.58 (m, 1H), 1.86 (m, 1H), 2.18 (m, 3H), 2.72 (m, 2H), 2.87 (t, 1H), 2.97 (dd, 1H), 3.24 (dd, 1H, J = 7, 9 Hz), 3.60 (dd, 1H, J = 8, 9 Hz), 3.82 (s, 3H), 6.63 (d, 1H, J = 8 Hz), 6.72 (d, 1H, J = 8 Hz), 7.11 (t, 1H, J = 8 Hz). MS (DCI/NH_3) *m/e* 204 $(M + H)^+$, *m/e* 221 $(M + NH_4)^+$. Anal. ($C_{13}H_{18}ClNO$) C, H, N.

***cis*-7-Methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]isoindole Hydrochloride (6b).** 6-Methoxy-3,4-dihydronaphthalene-1-carbonitrile **2b**[16] was treated following the procedure described for **6a** to yield **6b**, mp 149−52 °C. ^{1}H NMR ($CDCl_3$) (free base) δ 1.6 (m, 1H), 1.8 (m, 1H), 2.5 (m, 1H), 2.7 (m, 3H), 2.8 (dd, 1H, J = 4.5, 12), 3.2 (q, 1H, J = 9), 3.4 (dd, 1H, J = 7, 11), 3.5 (dd, 1H, J = 8, 11), 3.8 (s, 3H), 6.6 (d, 1H, J = 2), 6.7 (dd, 1H, J = 2, 9 Hz), 7.0 (d, 1H, J = 9 Hz). MS (DCI/NH_3), *m/e* 204 $(M + H)^+$. Anal. ($C_{13}H_{18}ClNO$) C, H, N.

***cis*-8-Methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]isoindole Hydrochloride (6c).** 7-Methoxy-3,4-dihydronaphthalene-1-carbonitrile **2b**[16] was treated following the procedure described for **6a** to yield **6c**, mp 231−233 °C. ^{1}H NMR ($CDCl_3$) (free base) δ 1.58 (m, 1H), 1.75 (m, 1H), 2.5−2.7 (m, 3H), 2.88 (m, 1H), 3.05 (m, 1H), 3.42 (m, 3H), 3.72 (s, 3H), 6.73 (dd, 1H), 6.8 (d, 1H), 7.04 (d, 1H). MS (DCI/NH_3) *m/e* 204 $(M + H)^+$. Anal. ($C_{13}H_{18}ClNO$) C, H, N.

Ethyl (2-Methoxyphenyl)-2-oxo-3-carboethoxypentanoate (11). Potassium *tert*-butoxide (179 g, 1.51 mol) and Et_2O (600 mL) were cooled to 10 °C. Diethyl oxalate (257 mL, 1.89 mol, 1.5 equiv) and ethyl 2-methoxyphenyl butyrate (**10**) (280 g, 1.26 mol) were dissolved in Et_2O (600 mL) and added to the cold KOtBu slurry at such a rate as to maintain the reaction temperature below 25 °C. The ice bath was removed, and the reaction was allowed to stir at room temperature for 19 h. The reaction was quenched onto 1 kg of ice and extracted with Et_2O (2×). The combined organic extracts were washed with 1 N NaOH (2×), and the aqueous layers were combined. The aqueous layer was acidified with concentrated HCl to pH 1 and extracted with Et_2O. The Et_2O extract was washed with brine, dried ($MgSO_4$), and concentrated to yield 384 g (95%) of crude product, which was used in the next step without purification. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H), 1.37 (t, 3H), 2.10−2.35 (m, 2H), 2.6−2.8 (m, 2H), 3.81 (s, 3H), 4.0 (dd, 1H), 4.18 (q, 2H), 4.32 (q, 2H), 6.80−6.92 (m, 2H), 7.10−7.22 (m, 2H).

5-Methoxy-1,2,3,4-tetrahydronaphthalene-1,2-carboxylic Anhydride (12). The keto diester **11** (384 g, 1.20 mol) was added to an ice cold solution of 80% H_2SO_4 (3.1 L). The ice bath was removed, and the reaction was stirred at ambient temperature for 6 h. The reaction was then poured onto 3 kg of ice with vigorous stirring, and the resulting yellow solid was collected by filtration, washed with 1.5 L of H_2O, and dried. The product was recrystallized from 1:1 EtOAc:MeCN to yield 140 g (51%) of the intermediate dihydronaphthalene which was dissolved in EtOAc (1500 mL) and hydrogenated with 10% Pd/C (14 g) at 4 atm H_2 for 20 h. The reaction mixture was

filtered and the solvent evaporated. Recrystallization from EtOAc yielded 135 g (49%) of **12**, mp 138−140 °C. ^{1}H NMR ($CDCl_3$) δ 1.97 (m, 1H), 2.28 (m, 1H), 2.47 (m, 1H), 2.95 (m, 1H), 3.55 (m, 1H), 3.83 (s, 3H), 4.32 (d, 1H), 6.83 (d, 1H), 7.17 (d, 1H), 7.27 (t, 1H).

(3a*R*,9b*R*)-6-Methoxy-((*S*)-α-methylbenzyl)-2,3,3a,4,5,9b-[1*H*]-hexahydrobenz[*e*]isoindole-1,3-dione (13) and (3a*S*,9b*S*)-6-Methoxy-(*S*)-α-methylbenzyl)-2,3,3a,4,5,9b-[1*H*]-hexahydrobenz[*e*]isoindole-1,3-dione (13a). The anhydride **12** (48.8 g, 210 mmol) was combined with (*S*)-(−)-α-methylbenzylamine (28.1 g, 0.230 mmol) in xylene (200 mL), and the reaction was heated to reflux with water removal (Dean Stark trap) until the theoretical amount of water was removed. The reaction was then cooled and diluted with EtOAc (300 mL). The resulting solution was washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated to dryness. The resulting oily solid was triturated with Et_2O, and the resulting crystalline (3a*R*,9b*R*) product **13** was collected (28.14 g, 40%), mp 148−150 °C. The diastereomeric purity of the imide was determined by HPLC (Chiracel OD column; 95:5 hexane:2-propanol; 1.0 mL/min) ^{1}H NMR ($CDCl_3$) δ 1.75 (d, 3H), 1.80 (m, 1H), 2.20 (m, 2H), 2.89 (m, 1H), 3.20 (m, 1H),3.80 (s, 3H), 3.95 (d, 1H), 5.49 (q, 1H), 6.79 (d, 1H), 7.17−7.45 (m, 7H). From the mother liquor, on cooling, a second crop was collected (16.8 g, 48%) and shown to be the (3a*S*,9b*S*) product **13a**, mp 101−103 °C. ^{1}H NMR ($CDCl_3$) δ 1.78 (d, 3H), 1.85 (m, 1H), 2.20 (m, 2H), 2.88 (m, 1H), 3.17 (m, 1H), 3.81 (s, 3H), 3.98 (d, 1H), 5.48 (q, 1H), 6.78 (d, 1H), 7.17−7.42 (m, 7H).

(3a*R*,9b*R*)-6-Methoxy-2,3,3a,4,5,9b-[1*H*]-hexahydrobenz[*e*]isoindole Hydrochloride (14). The imide **13** (28.0 g, 83.5 mmol) was dissolved in THF (100 mL) and added over 5 min to a 1.0 M solution of BH_3 in THF (417.5 mL). The reaction mixture was heated at reflux for 2 h, cooled to 25 °C, and treated cautiously with MeOH (100 mL). After the evolution of H_2 ceased, the solvent was evaporated at reduced pressure. The resulting oil was dissolved in 2:1 MeOH:IPA saturated with HCl(g), and the resulting solution was heated at reflux for 3 h. The solvent was removed in vacuo, the resulting solid was triturated with 1:1 EtOH:Et_2O, and the amine hydrochloride (25.8 g, 90%) was collected by filtration, mp 229−231 °C. The diastereomeric purity of the amine was determined by HPLC (Chiracel OD column; 99:1 hexane:2-propanol, 0.1% diethylamine; 0.5 mL/min). Absolute stereochemistry was determined by single-crystal X-ray of the amine hydrochloride salt. ^{1}H NMR ($CDCl_3$) (free base) δ 1.38 (d, 3H), 1.49 (m, 1H), 1.57 (m, 1H), 2.07 (dd, 1H), 2.15 (m, 1H), 2.40−2.72 (m, 3H), 2.97 (dd, 1H), 3.21 (q, 1H), 3.49 (m, 2H), 3.81 (s, 3H), 6.68 (d, 1H), 6.77 (d, 1H), 7.11 (t, 1H), 7.19−7.38 (m, 5H).

The intermediate *N*-benzylamine hydrochloride (25.7 g, 74.7 mmol) was dissolved in MeOH (700 mL), and 10% Pd/C (5.9 g) was added. The reaction was hydrogenated at 4 atm of H_2 at room temperature for 24 h to yield 15.9 g of **14** (89%) as a white solid, mp 223−225 °C. ^{1}H NMR (CD_3OD) δ 1.60 (m, 1H), 1.93 (m, 1H), 2.54 (m, 1H), 2.67 (m, 1H), 2.93 (m, 1H), 3.09 (dd, 1H), 3.13 (dd, 1H), 3.53 (m, 1H), 3.58 (dd, 1H), 3.67 (dd, 1H), 3.80 (s, 3H), 6.78 (d, 1H), 6.81 (d, 1H), 7.16 (t, 1H). $[\alpha]_D^{20}$ = −22.0° (*c* = 1.39, MeOH, free base).

(3a*S*,9b*S*)-6-Methoxy-2,3,3a,4,5,9b-[1*H*]-hexahydrobenz[*e*]isoindole Hydrochloride (14a). The imide **13a** (8.0 g, 23.8 mmol) was treated as described for compound **14** to yield the intermediate tertiary amine (7.2 g, 88%) as a white solid. ^{1}H NMR ($CDCl_3$) (free base) δ 1.38 (d, 3H), 1.52 (m, 1H), 1.72 (m, 1H), 2.02 (t, 1H), 2.18 (dd, 1H), 2.50−2.72 (m, 3H), 2.99 (t, 1H), 3.18 (q, 1H), 3.30−3.48 (m, 2H), 3.80 (s, 3H), 6.62 (d, 1H), 6.65 (d, 1H), 7.04 (t, 1H), 7.20−7.35 (m, 5H).

The tertiary amine (5.7 g, 16.6 mmol) was treated as described for the compound **14** to yield the title compound **14a** (3.10 g, 78%) as a white solid, mp 222−225 °C. ^{1}H NMR (CD_3OD) δ 1.60 (m, 1H), 1.93 (m, 1H), 2.54 (m, 1H), 2.67 (m, 1H), 2.93 (m, 1H), 3.09 (dd, 1H), 3.13 (dd, 1H), 3.53 (m, 1H), 3.58 (dd, 1H), 3.67 (dd, 1H), 3.80 (s, 3H), 6.78 (d, 1H), 6.81 (d, 1H), 7.16 (t, 1H). $[\alpha]_D^{25}$ = 22.2 (*c* = 1.265, MeOH, free base).

(3a*R*,9b*R*)-2-Aminoethyl-6-methoxy-2,3,3a,4,5,9b-[1*H*]-hexahydrobenz[*e*]isoindole (15). To the free base isolated from **14** (2.39 g, 10.0 mmol), dissolved in MeCN (10 mL) and diisopropylethylamine (5 mL) was added 0.67 mL (10.6 mmol) of chloroacetonitrile. The reaction was heated at 70 °C for 1 h, quenched in 5% $NaHCO_3$, and extracted with EtOAc (2×). The organic extracts were washed with water (2×) and brine (1×), dried (Na_2SO_4), and evaporated to yield 2.20 g of the intermediate nitrile as an off-white solid (90.5%). ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 1H), 2.58 (m, 3H), 2.77 (m, 1H), 3.23 (m, 2H), 3.48 (q, 1H), 3.64 (s, 2H), 3.81 (s, 3H), 6.70 (d, 1H), 6.74 (d, 1H), 7.12 (t, 1H).

To $LiAlH_4$ (0.82 g, 21.5 mmol) suspended in THF (30 mL) at 0 °C was added dropwise a solution of nitrile (0.80 g, 3.30 mmol) dissolved in THF (5 mL). The reaction was then stirred at room temperature for 1.5 h, quenched by addition of H_2O (0.8 mL), 15% NaOH (0.8 mL), and H_2O (2.4 mL), filtered through Celite, and washed with several hot portions of THF, and the solvent was evaporated to yield **15** (0.75 g, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 3H), 1.72 (m, 1H), 2.19 (m, 2H), 2.52 (m, 3H), 2.70 (m, 1H), 2.80 (t, 1H), 3.21 (dd, 1H), 3.28 (t, 1H), 3.40 (m, 1H), 3.80 (s, 3H), 6.67 (d, 1H), 6.75 (d, 1H), 7.11 (t, 1H).

***cis*-6-Methoxy-(2-(2-aminoethyl))-2,3,3a,4,5,9b-[1*H*]-hexahydrobenz[*e*]isoindole (7a).** From the free base of 6a (4.5 g, 22.16 mmol), following the procedure for **15**, was isolated **7a** (4.3 g, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 3H), 1.72 (m, 1H), 2.19 (m, 2H), 2.52 (m, 3H), 2.70 (m, 1H), 2.80 (t, 1H), 3.21 (dd, 1H), 3.28 (t, 1H, 3.40 (m, 1H), 3.80 (s, 3H), 6.67 (d, 1H), 6.75 (d, 1H), 7.11 (t, 1H).

***trans*-6-Methoxy-(2-(2-aminoethyl))-2,3,3a,4,5,9b-[1*H*]-hexahydrobenz[*e*]isoindole (9a).** From the free base of **8a** (1.5 g, 7.4 mmol) following the procedure for **15**, was isolated **8a** (1.19 g, 65%) as a colorless oil.

Method A. Method A is exemplified by the following procedure for **18**.

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl][1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (18). *N*-(2-Chloroethyl)-*N*′-[3-[(2-methoxycarbonyl)benzothienyl]]-urea **17a**[15] (0.625 g, 2.00 mmol), **6a** (0.503 g, 2.1 mmol), and diisopropylethylamine (0.35 mL, 2.0 mmol) were combined in DMSO (1 mL) and heated at 100 °C for 3 h. The reaction was cooled, and EtOH (3 mL) was added. The crystalline product was collected and converted to its HCl salt to yield **18** (0.312 g) as a white solid, mp >255 °C (MeOH). ^{1}H NMR (DMSO-d_6) (free base) δ 1.45 (m, 1H), 1.53 (m, 1H), 2.10−2.80 (m, 6H), 3.10−3.45 (m, 4H), 3.74 (s, 3H), 4.04 (t, 2H), 6.73 (d, 2H), 7.07 (t, 1H), 7.55 (t, 1H), 7.63 (t, 1H), 8.10 (d, 1H), 8.39 (d, 1H), 12.50 (s, 1H). MS (DCI/NH_3) *m/e* 448 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_3S\cdot HCl\cdot 0.75H_2O$) C, H, N.

3-[2-(*trans*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (21). The chloroethyl urea **17a** (0.40 g, 1.22 mmol)[15] and **8a** (0.24 g, 1.2 mmol) were treated by method A to yield **21** as a white solid (0.064 g, 11%), mp >250 °C (MeOH-DMF/Et_2O). ^{1}H NMR (DMSO-d_6) δ 1.61 (m, 1H), 1.93 (m, 1H), 2.16 (m, 2H), 2.67 (m, 2H), 2.88 (m, 1H), 3.70 (m, 2H), 3.78 (s, 3H), 3.93 (m, 1H), 4.03 (m, 1H), 4.32 (m, 3H), 6.66 (m, 1H), 6.88 (d, 1H, *J* = 8,4 Hz), 7.17 (t, 1H, *J* = 7.9 Hz), 7.62 (m, 2H), 8.13 (d, 1H, *J* = 8.1 Hz), 8.43 (d, 1H, *J* = 8.1 Hz), 10.27 (br. s, 1H), 12.67 (br s, 1H). MS (DCI/NH_3) *m/e* 448 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_3S\cdot HCl\cdot 0.25H_2O$) C, H, N.

Method B. Method B is exemplified by the following procedure for **22**.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (22). 3-Amino-2-carbomethoxy-benzothiophene[15] (2.21 g, 10 mmol) and triphosgene (0.99 g, 3.33 mmol) were combined in toluene (40 mL) and heated at reflux for 3 h. The solvent was then evaporated to yield the intermediate isocyanate (2.45 g) as a white solid. The amine **15** (0.24 g, 1.0 mmol) and the obtained

isocyanate (0.260 g, 1.1 mmol) were combined in toluene (10 mL) and heated at reflux for 3 h. The product was then partitioned between 5% $NaHCO_3$ and hot EtOAc, and the organic phase was dried (K_2CO_3), filtered, and evaporated. The resulting product was converted to its HCl salt and recrystallized from EtOH−Et_2O to yield 0.28 g of 22 as a white solid, mp >250 °C (dec). ^{1}H NMR (CD_3OD) δ 1.62−1.71 (m, 1H), 1.89−1.97 (m, 1H), 2.54−2.62 (m, 1H), 2.76−2.88 (m, 1H), 3.13−3.51 (m, 2H), 3.60 (t, 2H), 3.63−3.71 (m, 1H), 3.80 (s, 3H), 3.84−4.19 (m, 2H), 4.42 (dt, 2H), 6.80 (t, 2H), 7.16 (t, 1H), 7.53 (t, 1H), 7.63 (t, 1H), 7.98 (d, 1H), 8.18 (d, 1H). MS (DCI/NH_3) *m/e* 448 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_3S\cdot HCl\cdot H_2O$) C, H, N.

3-[2-((3a*S*,9b*S*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (23). The chloroethyl urea 17a (1.50 g, 4.57 mmol) and the free base of 14a (0.450 g, 1.85 mmol) were treated by method A to yield **23** as a white solid, mp >250 °C. ^{1}H NMR (CD_3OD) δ 1.60−1.77 (m, 1H), 1.88−2.02 (m, 1H), 2.52−2.67 (m, 1H), 2.74−2.92 (m, 2H), 3.27−3.50 (m, 2H), 3.58−3.73 (m, 3H), 3.81 (s, 3H), 3.93−4.19 (m, 2H), 4.43 (t, 2H), 6.81 (t, 2H), 7.18 (t, 1H), 7.54 (t, 1H), 7.64 (t, 1H), 7.99 (d, 1H), 8.19 (d, 1H). MS (DCI/NH_3) *m/e* 448 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_3S\cdot HCl$) C, H, N.

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]benzofuro[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione Hydrochloride (19). The chloroethyl urea **16b**[15] (0.390 g, 1.65 mmol) and **6a** (0.497 g, 1.60 mmol) were treated by method A to yield **19** (0.291 g) as a white solid, mp 252 °C. ^{1}H NMR (CD_3OD) δ 1.65 (m, 1H), 1.95 (m, 1H), 2.50−3.15 (m, 6H), 3.40−3.75 (m, 3H), 3.60 (t, 2H), 3.81 (s, 3H), 4.42 (t, 2H), 6.80 (d, 1H), 6.83 (d, 1H), 7.17 (t, 1H), 7.45 (m, 1H), 7.69 (m, 2H), 7.94 (d, 1H). MS (DCI/NH_3) *m/e* 432 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_4\cdot HCl\cdot 0.5H_2O$) C, H, N.

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-1*H*-pyrimido[5,4-*b*]indole-2,4-(3*H*,5*H*)-dione Hydrochloride (20). 2-Carboethoxy-3-aminoindole[15] (0.18 g, 0.85 mmol) and the amine **7a** (0.19 g, 0.77 mmol) were treated by method B. The resulting product was collected by filtration and dissolved in 15 mL of EtOH and 5 mL of THF. To this solution was added 0.58 mL of 1.0 M KOtBu in THF, and the mixture was heated at reflux for 45 min. After cooling, the product was collected by filtration and converted to its HCl salt to yield **20** (0.12 g, 61%), mp >250 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.52−1.66 (m, 1H), 1.74−1.84 (m, 1H), 2.36−2.52 (m, 1H), 2.62−2.82 (m, 2H), 2.97−3.08 (m, 1H), 3.42−3.57 (m, 3H), 3.64−3.86 (m, 1H), 3.77 (s 3H), 4.02−4.34 (m, 4H), 6.72−6.86 (m, 2H), 7.09−7.19 (m, 2H), 7.36−7.45 (m, 2H), 7.96 (t, 1H), 9.91 and 10.27 (bs and bs, 1H), 11.81 and 12.10 (d and d, 2H). MS (DCI/NH_3) *m/e* 431 $(M + H)^+$. Anal. ($C_{25}H_{26}N_4O_3\cdot HCl\cdot 0.5H_2O$) C, H, N.

3-[2-(*cis*-7-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (24). The chloroethyl urea **17a** (1.21 g, 3.7 mmol)[15] and **6b** (1.0 g, 4.17 mmol) were reacted by method A to yield **24** as a white solid, mp 241−2 °C. ^{1}H NMR (DMSO-d_6) (free base) δ 1.48 (m, 1H), 1.63 (m, 1H), 2.08 (m, 1H), 2.21 (m, 1H), 2.5−2.7 (m, 4H), 3.10−3.4 (m, 4H), 3.68 (s, 3H), 4.04 (t, 2H), 6.68 (m, 2H), 7.01 (d, 1H), 7.52 (t, 1H), 7.61 (t, 1H), 8.11 (d, 1H), 8.39 (d, 1H), 12.50 (s, 1H). MS (DCI/NH_3) *m/e* 448 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_3S\cdot HCl$) C, H, N.

3-[2-(*cis*-8-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (25). The chloroethyl urea 17a 15 (0.5 g, 1.53 mmol) and 6c (0.3 g, 1.47 mmol) were reacted by method A to yield 25 as a white solid, mp > 250 °C. ^{1}H NMR (DMSO-d_6) (free base) δ 1.48 (m, 1H), 1.63 (m, 1H), 2.15 (m, 1 H), 2.22 (m, 1H), 2.41−2.74 (4 H), 3.16−3.36 (m, 4H), 3.69 (s, 3H), 4.05 (t, 2H), 6.64 (m, 2H), 6.90 (d, 1H), 7.55 (t, 1H), 7.63 (t, 1H), 8.11 (d, 1H), 8.39 (d, 1H), 12.53 (s, 1H). MS (DCI/NH_3) *m/e* 448 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_3S\cdot HCl$) C, H, N.

3-[2-(*cis*-9-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (26). The chloroethyl urea **17a**[15] (0.41 g, 1.25 mmol) and *cis*-9-methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindole **18** (0.33 g, 1.37 mmol) were reacted by method A to yield 0.17 g of **26** as a white solid, mp 214−16 °C. ^{1}H NMR (CD_3OD) δ 1.73 (m, 1H), 1.91 (m, 1H), 2.78 (m, 4H), 3.00−4.40 (m, 4H), 3.62 (t, 2H), 3.83 (s, 3H), 4.43 (t, 2H), 6.76 (d, 1H), 6.81 (d, 1H), 7.16 (t, 1H), 7.55 (t, 1H), 7.66 (t, 1H), 8.00 (d, 1H), 8.19 (d, 1H). MS (DCI/NH_3) *m/e* 448 $(M + H)^+$. Anal. ($C_{25}H_{25}N_3O_3S\cdot HCl\cdot 0.5H_2O$) C, H, N.

3-[3-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)propyl]-[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (27). *N*-(3-Chloropropyl)-*N*′-[3-[(2-methoxycarbonyl)benzothienyl]urea (0.613 g, 1.80 mmol) prepared by the method of Romeo,[15] substituting for 3-chloropropylisocyanate, and compound **6a** (0.369 g, 1.82 mmol) were reacted by method A to yield 0.10 g of **27** as a white solid, mp 183−6 °C. ^{1}H NMR (CD_3OD) δ 1.65 (m, 1H), 1.92 (m, 1H), 2.18 (m, 2H), 2.57 (m, 1H), 2.70−3.40 (m, 6H), 3.55−4.10 (m, 3H), 3.80 (s, 3H), 4.18 (t, 2H), 6.78 (d, 1H), 7.02 (d, 1H), 7.16 (t, 1H), 7.53 (t, 1H), 7.63 (t, 1H), 7.98 (d, 1H), 8.18 (d, 1H). MS (DCI/NH_3) *m/e* 462 $(M + H)^+$. Anal. ($C_{26}H_{27}N_3O_3S\cdot HCl\cdot 0.25H_2O$) C, H, N.

3-[4-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)butyl]-[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (28). 5-Methoxy-1,2,3,4-tetrahydronaphthalene-*cis*-1,2-dicarboxylic acid diethyl ester (37.0 g, 129 mmol)[17] was dissolved in THF (100 mL) and added over 15 min to a suspension of $LiAlH_4$ (9.20 g, 241 mmol) in THF (400 mL). The reaction was stirred at 25 °C for 18 h and then quenched by sequential addition of 9.2 mL of H_2O, 9.2 mL of 15% aqueous KOH solution, and 29 mL of H_2O. The reaction was filtered and the solvent evaporated at reduced pressure to yield *cis*-5-methoxy-1,2- bis(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (22.15 g, 82%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 2H), 2.04 (m, 1H), 2.53 (br s, 1H), 2.85 (m, 2H), 3.02 (br s, 1H), 3.48 (m, 1H), 3.65−3.85 (m, 4H), 3.86 (s, 3H), 6.70 (d, 1H), 6.73 (d, 1H), 7.12 (t, 1H).

cis-5-Methoxy-1,2-bis(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (22.2 g, 100 mmol), triethylamine (84 mL, 600 mmol), and CH_2Cl_2 (500 mL) were combined and cooled to 0 °C. Methanesulfonyl chloride (23.3 mL, 300 mmol) was added over 15 min, and the reaction was stirred an additional 1.5 h. The reaction was quenched in 5% aqueous $NaHCO_3$, the organic phase washed with one additional portion of 5% aqueous $NaHCO_3$ and brine, then dried ($MgSO_4$), and filtered, and solvent evaporated. The crude product was triturated with cold Et_2O and then collected by filtration to yield *cis*-5-methoxy-1,2(bishydroxymethyl)-1,2,3,4-tetrahydronaphthalene-1,2-bis-mesylate (33.5 g, 94%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.65−1.95 (m, 2H), 2.33 (m, 1H), 2.88 (m, 1H), 2.97 (s, 3H), 3.09 (s, 3H), 3.12 (m, 1H), 3.70 (m, 1H), 3.88 (s, 3H), 4.40 (m, 4H), 6.72 (d, 1H), 6.76 (d, 1H), 7.18 (t, 1H).

The bis-mesylate intermediate (1.89 g, 5.0 mmol) was dissolved in 1,4-diaminobutane (15 mL), and the reaction was heated at 65 °C for 3 h. The reaction was quenched in 5% aqueous NaOH and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried (K_2CO_3), filtered, and evaporated to yield *cis*-6-methoxy-2-(4-aminobutyl)-2,3,3a,4,5,9b-[1*H*]-hexahydrobenz[*e*]isoindole as a colorless oil (1.20 g, 85%). ^{1}H NMR ($CDCl_3$) δ 1.40−1.85 (m, 6H), 2.12 (m, 2H), 2.40−2.68 (m, 5H), 2.71 (t, 2H), 3.23−3.5 (m, 4H), 3.70 (m, 1H), 3.82 (s, 3H), 6.68 (d, 1H), 6.75 (d, 1H), 7.11 (t, 1H).

The intermediate primary amine (0.24 g, 0.87 mmol) and the benzothiophene 16 were treated by method B to yield **28** (0.28 g, 67%) as a white solid, mp 173−175 °C. ^{1}H NMR (DMSO-d_6) (free base) δ 1.36−1.52 (m, 3H), 1.57−1.69 (m, 3H), 2.05 (t, 1H), 2.11 (dd, 1H), 2.34−2.62 (m, 5H), 3.06 (t, 1H), 3.15 (t, 1H), 3.26 (q, 1H), 3.74 (s, 3H), 3.92 (t, 2H), 6.71 (t, 2H), 7.05 (t, 1H), 7.55 (t, 1H), 7.63 (dt, 1H), 8.10 (d, 1H), 8.38 (d, 1H). MS (DCI/NH_3) *m/e* 476 $(M + H)^+$. Anal. ($C_{27}H_{29}N_3O_3S\cdot HCl\cdot H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-7-cyano[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (29). Nitroterephthalonitrile (5.0 g, 28.9 mmol)[26] was refluxed in MeOH with methyl thioglycolate (3.06 g, 28.9 mmol) and Na_2CO_3 (3.06 g, 28.9 mmol) for 3 h. The reaction mixture was cooled to room temperature, quenched with water, and concentrated. The residue was chromatographed on silica gel, eluting with 4:1, then 1:1 hexane:EtOAc to yield 3-amino-2-carbomethoxy-6-cyano-benzothiophene (5.50 g, 82%). ^{1}H NMR (DMSO-d_6) δ 8.50 (s, 1H), 8.32 (d, 1H), 7.80 (dd, 1H), 7.29 (br s, 2H), 3.81 (s, 3H). MS (DCI/NH_3) *m/e* 250 $(M + NH_4)^+$.

3-Amino-2-carbomethoxy-6-cyano-benzothiophene (0.465 g, 2.0 mmol) and the amine **15** (0.39 g, 1.6 mmol) were reacted by method B. The crude product was purified by chromatography on silica gel, eluting with EtOAc:HCOOH:H_2O (18:1:1) and converted to the HCl salt to yield 29 (0.28 g, 34%). ^{1}H NMR (DMSO-d_6) δ 12.87 (d, 1H), 10.82 (s, 1H), 8.78 (s, 1H), 8.56 (d, 1H), 7.97 (d, 1H), 7.17 (t, 1H), 6.71−6.86 (m, 2H), 4.29 (m, 2H), 4.15 (m, 1H), 4.01 (m, 1H), 3.78 (s, 3H), 3.51 (m, 2H), 3.02 (m, 1H), 2.58−2.82 (m, 3H), 1.79 (m, 2H), 1.61 (m, 2H). MS (DCI/NH_3) *m/e* 473 $(M + H)^+$. Anal. ($C_{26}H_{24}N_4O_3S$·2HCl·0.5H_2O) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-7-carboxamido[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (30). 3-Amino-2-carbomethoxy-6-cyano-benzothiophene (2.46 g, 10.6 mmol) and ground KOH (7.12 g, 127 mmol) were taken up in *tert*-butyl alcohol (80 mL) to form a slurry, which was refluxed for 24 h. The mixture was cooled, poured into water, and the solution adjusted to pH 3 with 37% HCl. The resulting mixture was filtered, and the crude amido acid was dissolved in DMSO (125 mL) and MeOH (75 mL) and stirred at room temperature. A 2.0 M solution of trimethylsilyldiazomethane ($TMSCHN_2$) in hexanes (8 mL) was added slowly. The reaction was stirred an additional 10 min and condensed in vacuo. The crude product was chromatographed on silica gel eluting with EtOAc, and the residue was recrystallized from MeOH/EtOAc to yield 0.90 g (34%) of 3-amino-2-carbomethoxy-6-carboxamido-benzothiophene. ^{1}H NMR (DMSO-d_6) δ 8.32 (d, 1H), 8.21 (d, 1H), 8.11 (br s, 1H), 7.88 (dd, 1H), 7.52 (br s, 1H), 7.22 (br s, 2H), 3.81 (s, 3H). MS (DCI/NH_3) *m/e* 268 $(M + NH_4)^+$.

The obtained benzothiophene (0.45 g, 1.7 mmol) and the amine **15** (0.369 g, 1.5 mmol) were treated by method B to yield the free base, which was taken up in 4.0 M HCl in dioxane, and triturated with EtOH to give **31** (0.191 g, 24%), mp >270 °C. ^{1}H NMR (DMSO-d_6) δ 12.88 (d, 1H), 10.48 (s, 1H), 8.60 (s, 1H), 8.46 (dd, 1H), 8.20 (s, 1H), 8.02 (dd, 1H), 7.62 (s, 1H), 7.17 (t, 1H), 6.72−6.87 (m, 2H), 4.29 (m, 2H), 4.16 (m, 1H), 4.02 (m, 1H), 3.78 (s, 3H), 3.51 (m, 2H), 3.02 (m, 1H), 2.60−2.85 (m, 3H), 1.79 (m, 2H), 1.61 (m, 2H). MS (DCI/NH_3) *m/e* 491 $(M + H)^+$. Anal. ($C_{26}H_{26}N_4O_4S$·2HCl·0.75H_2O) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-7-trifluoromethyl[1]-benzothieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (31). 6-Trifluoromethyl-3-amino-2-ethoxycarbonyl-benzothiophene (0.556 g, 1.49 mmol), prepared by the method of J. R. Beck[20] from 4-trifluoromethyl-2-nitrobenzonitrile and ethylthioglycolate, was converted to the corresponding isocyanate by method B. The resulting isocynate was reacted with the amine **15** (1.24 mmol) in the presence of Et_3N (1.2 equiv, 0.21 mL) in toluene (10 mL) at reflux for 18 h to yield **30** (0.292 g, 43%), mp >270 °C. $[\alpha]_D = +30.6°$ ($c = 0.54$, EtOH). ^{1}H NMR (DMSO-d_6) δ 12.82 (br s, 1H), 8.70 (s, 1H), 8.63 (d, 1H), 7.93 (d, 1H), 7.17 (t, 1H), 6.84 (br d, 1H), 6.75 (br d, 1H), 4.29 (m, 2H), 4.17 (m, 1H), 4.04 (m, 1H), 3.77 (s, 3H), 3.52 (m, 3H), 3.04 (m, 2H), 2.70 (m, 2H), 2.43 (m, 1H), 1.78 (m, 1H), 1.59 (m, 1H). MS (DCI/NH_3) *m/e* 516 $(M + H)^+$. Anal. ($C_{26}H_{24}F_3N_3O_3S$·HCl·0.5H_2O) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-cyano[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (32). 4-Chloroisophthalonitrile (5.69 g, 35 mmol), prepared by the method of Markley[27] was treated with methyl thioglycolate (3.95 g, 35 mmol) and Na_2CO_3 (3.7 g, 35 mmol) in MeOH by the procedure described for **29** to yield 3-amino-2-carbomethoxy-5-cyano-benzothiophene (3.00 g, 37%), mp 248 °C. ^{1}H NMR (DMSO-d_6) δ 8.71 (s, 1H), 8.09 (d, 1H), 7.86 (dd, 1H), 7.30 (br s, 2H), 3.81 (s, 3H). MS (DCI/NH_3) *m/e* 250 $(M + NH_4)^+$.

The obtained benzothiophene (0.46 g, 2.0 mmol) and the amine 15 (0.39 g, 1.6 mmol) were treated by method B to yield 32 (0.68 g, 83%). ^{1}H NMR (DMSO-d_6) δ 1.61 (m, 2H), 1.79 (m, 2H), 2.59−2.83 (m, 3H), 3.02 (m, 1H), 3.52 (m, 2H), 3.78 (s, 3H), 4.01 (m, 1H), 4.14 (m, 1H), 4.29 (m, 2H), 6.71−6.86 (m, 2H), 7.17 (t, 1H), 8.02 (d, 1H), 8.39 (d, 1H), 8.90 (d, 1H), 10.69 (s, 1H), 12.82 (d, 1H). MS (DCI/NH_3) *m/e* 473 $(M + H)^+$. Anal. ($C_{26}H_{24}N_4O_3S$·2HCl·0.25H_2O) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-carbomethoxy[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (33). 3-Amino-4-chlorobenzoic acid (18.72 g, 109.1 mmol) was added to a mixture of H_2O (200 mL) and 37% HCl (35 mL), and the resulting slurry was cooled to 5 °C. A solution of $NaNO_2$ (8.65 g, 125 mmol) in H_2O (70 mL) was added dropwise, and the solution was stirred at 5 °C for 30 min. The solution was then added to a slurry consisting of H_2O (400 mL), CuCN (9.85 g, 109 mmol), and KCN (12.06 g, 185 mmol), while maintaining the temperature at 5−10 °C. The mixture was stirred at 10 °C for another 30 min and then heated to 80 °C for 1 h. The reaction was cooled, and the pH adjusted to ∼1 by addition of concentrated HCl. The solution was extracted with $CHCl_3$ (5×), and the combined extracts were rinsed with 1 M HCl, brine, and dried ($MgSO_4$). The solvent was removed in vacuo, and the crude product was recrystallized from $CHCl_3$/EtOAc to yield 15.9 g (80%) of 3-cyano-4-chloro-benzoic acid, mp 180 °C. ^{1}H NMR ($CDCl_3$) δ 10.55 (br s, 1H), 8.42 (d, 1H), 8.26 (dd, 1H), 7.68 (d, 1H). MS (DCI/NH_3) *m/e* 213 $(M + NH_4)^+$.

3-Cyano-4-chloro-benzoic acid (4.83 g, 26.6 mmol) was dissolved in 1:1 EtOAc/MeOH (150 mL) then treated slowly with a 2.0 M solution of trimethylsilyldiazomethane ($TMSCHN_2$) in hexanes (25 mL) at room temperature. The reaction mixture was stirred an additional 10 min, and concentrated in vacuo. The residue was recrystallized from hexane/EtOAc to yield 3.19 g (61%) of methyl-3-cyano-4-chloro-benzoate, mp 193 °C. ^{1}H NMR ($CDCl_3$) δ 8.34 (d, 1H), 8.19 (dd, 1H), 7.52 (d, 1H), 3.97 (s, 3H). MS (DCI/NH_3) *m/e* 199 $(M + NH_4)^+$.

Methyl-3-cyano-4-chloro-benzoate (3.19 g, 16.3 mmol) was treated with methyl thioglycolate (1.73 g, 16.3 mmol) and Na_2CO_3 (1.72 g, 16.3 mmol) in MeOH by the procedure described for **29** to yield 3-amino-2,5-carbomethoxy-benzo[*b*]thiophene (2.78 g, 64%), mp 193 °C. ^{1}H NMR (300 MHz, DMSO) δ 8.88 (d, 1H), 8.03 (dd, 1H), 7.97 (d, 1H), 7.39 (br s, 2H), 3.91 (s, 3H), 3.80 (s, 3H). MS (DCI/NH_3) *m/e* 283 $(M + NH_4)^+$. This intermediate (0.58 g, 2.0 mmol) and the amine 15 (0.30 g, 1.2 mmol) were treated by method B to yield **33** (0.44 g, 68%), mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 12.83 (d, 1H), 10.50 (s, 1H), 9.19 (d, 1H), 8.28 (d, 1H), 8.14 (d, 1H), 7.17 (t, 1H), 6.72−6.86 (m, 2H), 4.29 (m, 2H), 4.15 (m, 1H), 4.02 (m, 1H), 3.78 (s, 3H), 3.52 (m, 2H), 3.02 (m, 1H), 2.58−2.84 (m, 3H), 1.80 (m, 2H), 1.61 (m, 2H). MS (DCI/NH_3) *m/e* 506 $(M + H)^+$. Anal. ($C_{27}H_{27}N_3O_5S$·HCl·1.5H_2O) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-*N*,*N*-dimethylcarboxamido[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (34). 3-Cyano-4-chlorobenzoic acid (5.55 g, 30.5 mol) in toluene (100 mL) was treated with oxalyl chloride (2.93 mL, 33.6 mmol) and pyridine (0.1 mL), and the solution was heated to reflux until HCl evolution ceased (6 h). The reaction was cooled and concentrated in vacuo. The resulting solution was poured into a stirred mixture of 40% aqueous dimethylamine (150 mL) and EtOAc (150 mL), and the reaction stirred for 10 min. The layers were separated, the aqueous layer was extracted with EtOAc (2×), and the combined organic layers were rinsed with 1 M HCl (2×) and brine and dried ($MgSO_4$). The solution was evaporated, and the residue was recrystallized from EtOAc to yield 4.91 g (77%)

of 3-cyano-4-chloro-*N*,*N*-dimethylbenzamide, mp 193 °C. ^{1}H NMR ($CDCl_3$) δ 8.28 (d, 1H), 7.61 (dd, 1H), 7.58 (d, 1H), 3.12 (br s, 2H), 3.00 (br s, 3H). MS (DCI/NH_3) *m/e* 226 $(M + NH_4)^+$.

3-Cyano-4-chloro-*N*,*N*-dimethylbenzamide (3.00 g, 14.4 mmol) was treated with methyl thioglycolate (1.53 g, 14.4 mmol) and Na_2CO_3 (1.52 g, 14.4 mmol) in MeOH by the procedure described in **29** to yield 3-amino-2-carbomethoxy-5-*N*,*N*-dimethylcarboxamido-benzo[*b*]thiophene (1.55 g, 39%), mp 218−220 °C. ^{1}H NMR (DMSO-d_6) δ 8.28 (d, 1H), 7.90 (dd, 1H), 7.54 (d, 1H), 7.23 (br s, 2H), 3.80 (s, 3H), 3.02 (br s, 3H), 2.98 (br s, 3H). MS (DCI/NH_3) *m/e* 296 $(M + NH_4)^+$.

The intermediate benzo[*b*]thiophene (0.556 g, 2.0 mmol) and the amine **15** (0.35 g, 1.42 mmol) were treated by method B to yield **34** (0.183 g, 23%), mp 216−219 °C. ^{1}H NMR (DMSO-d_6) δ 12.79 (d, 1H), 10.66 (s, 1H), 8.53 (d, 1H), 8.20 (d, 1H), 7.69 (d, 1H), 7.17 (t, 1H), 6.72−6.87 (m, 2H), 4.29 (m, 2H), 4.15 (m, 1H), 4.02 (m, 1H), 3.78 (s, 3H), 3.55 (m, 2H), 3.04 (s, 3H), 3.02 (m, 1H), 2.92 (s, 3H), 2.60−2.85 (m, 3H), 1.80 (m, 2H), 1.62 (m, 2H). MS (DCI/NH_3) *m/e* 519 $(M + H)^+$. Anal. ($C_{28}H_{30}N_4O_4S\cdot 2HCl\cdot H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]]-8-nitro[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (35). 2-Chloro-5-nitrobenzonitrile (25.0 g, 136.9 mmol) was treated with ethyl thioglycolate (16.45, 136.9 mmol) and K_2CO_3 (19 g, 136.9) in EtOH according to the method of example **29** to yield 3-amino-2-carbomethoxy-5-nitro-benzothiophene (19.68 g, 54%), mp 208−210 °C. ^{1}H NMR (DMSO-d_6) δ 9.23 (d, 1H), 8.29 (d, 1H), 8.11 (dd, 1H), 7.45 (br s, 2H), 4.29 (q, 2H), 1.31 (t, 3H). MS (DCI/NH_3) *m/e* 284 $(M + NH_4)^+$.

The intermediate benzo[*b*]thiophene (0.532 g, 1.9 mmol) and the amine 15 (0.418 g, 1.7 mmol) were treated by method B to yield **35** (0.329 g, 37%), mp 298−305 °C. ^{1}H NMR (DMSO-d_6) δ 12.93 (d, 1H), 10.37 (s, 1H), 9.48 (d, 1H), 8.42 (s, 2H), 7.17 (t, 1H), 6.72−6.86 (m, 2H), 4.29 (m, 2H), 4.15 (m, 1H), 4.02 (m, 1H), 3.78 (s, 3H), 3.52 (m, 2H), 3.02 (m, 1H), 2.59−2.86 (m, 3H), 1.79 (m, 2H), 1.61 (m, 2H). MS (DCI/NH_3) *m/e* 493 $(M + H)^+$. Anal. ($C_{25}H_{24}N_4O_5S\cdot HCl$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]- 8-methyl[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (36). 5-Methyl-3-amino-2-caroboethoxybenzothiophene[28] (1.0 g, 4.26 mmol) and the amine **15** (0.350 g, 1.45 mmol) were treated by method B to yield **36** (0.340 g, 52%) as a white solid, mp 196−198 °C; $[\alpha]_D$ +27.8° (*c* = 0.66, MeOH). ^{1}H NMR (MeOD) δ 1.20 (m, 1H), 1.40 (m, 2H), 2.1.(m, 1H), 2.50 (s, 3H), 2.65 (m, 2H), 3.10 (m, 2H), 3.58 (m, 2H), 3.74 (s, 3H), 3.84 (m, 2H), 4.12 (m, 2H), 6.75 (q, 2H), 7.02 (t, 1H), 7.40 (m, 1H), 7.75 (m, 1H), 7.90 (d, 1H). MS (DCI/NH_3) *m/e* 462 $(M + H)^+$. Anal. ($C_{26}H_{28}ClN_3O_3S\cdot HCl\cdot 0.25H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-carboxamido[1]benzothieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (37). 3-Cyano-4-chlorobenzoic acid (5.55 g, 30.5 mmol) was treated with oxalyl chloride (2.93 mL, 33.6 mmol) by the procedure described for example 34. The resulting acid chloride was poured into a stirred mixture of saturated aqueous NH_4OH (150 mL) and EtOAc (150 mL), and the reaction was stirred for 10 min. The layers were separated, the aqueous layer was extracted with EtOAc (2×), and the combined organic layers were rinsed with 1 M HCl (2×) and brine and dried ($MgSO_4$). The solution was condensed, and the residue was recrystallized from EtOAc to yield 3.35 g (61%) of 3-cyano-4-chloro-benzamide, mp 193 °C. ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1H), 7.98 (dd, 1H), 7.63 (d, 1H), 5.50−6.20 (br s, 2H). MS (DCI/NH_3) *m/e* 198 $(M + NH_4)^+$.

The intermediate benzamide (3.30 g, 18.3 mmol) was converted by the procedure described for example **29** to 3-amino-2-carbomethoxy-5-carboxamido-benzo[*b*]thiophene (1.08 g, 30%), mp 248 °C. ^{1}H NMR (DMSO-d_6) δ 9.31 (d, 1H), 7.98 (dd, 1H), 7.96 (br s, 1H), 7.91 (d, 1H), 7.48 (br s, 1H), 7.21 (br s, 2H), 3.80 (s, 3H). MS (DCI/NH_3) *m/e* 268 $(M + NH_4)^+$.

The intermediate benzo[*b*]thiophene (0.25 g, 1.0 mmol) and the amine **15** (0.246 g, 1.0 mmol) were treated by method B to give **37** (0.117 g, 22%), mp >250 °C. ^{1}H NMR (DMSO-d_6) δ 12.72 (d, 1H), 11.20 (s, 1H), 9.08 (d, 1H), 8.19 (d, 1H), 8.10 (s, 1H), 8.08 (d, 1H), 7.56 (s, 1H), 7.17 (t, 1H), 6.72−6.87 (m, 2H), 4.29 (m, 2H), 4.14 (m, 1H), 4.01 (m, 1H), 3.78 (s, 3H), 3.51 (m, 2H), 3.01 (m, 1H), 2.58−2.85 (m, 3H), 1.79 (m, 2H), 1.62 (m, 2H). MS (DCI/NH_3) *m/e* 491 $(M + H)^+$. Anal. ($C_{26}H_{26}N_4O_4S\cdot HCl\cdot 0.75H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]- 8-chloro[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (38). 5-Chloro-3-amino-2-carboethoxybenzothiophene[34] (0.52 g, 2.03 mmol) and the amine **15** (0.417 g, 1.69 mmol) were treated by method B to yield **38** (0.273 g, 32%) as a white solid, mp >210 °C. ^{1}H NMR (DMSO-d_6) δ 12.65 (m, 1H), 8.54 (m, 1H), 8.19 (m, 1H), 7.70 (m, 1H), 7.17 (m, 1H), 6.84 (m, 1H), 6.76 (m, 1H), 4.28 (m, 2H), 4.18 (m, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 3.52 (m, 3H), 3.03 (m, 2H), 2.74 (m, 2H), 2.45 (m, 1H), 1.80 (m, 1H), 1.62 (m, 1H). MS (DCI/NH_3) *m/e* 482 $(M + H)^+$. Anal. ($C_{25}H_{25}Cl_2N_3O_3S\cdot HCl\cdot 2H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-9-chloro[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (39). 4-Chloro-3-amino-2-carboethoxybenzothiophene was prepared as described by De Angelis[28] from 2,6-dichlorobenzonitrile and ethyl thioglycolate. The resulting benzothiophene (1.0 g, 4.17 mmol) and the amine **15** (1.65 mmol) were treated by method B to yield **39** (0.273 g, 32%) as a white solid, mp >270 °C; $[\alpha]_D$ +25.7° (c = 0.51 in MeOH). ^{1}H NMR (DMSO-d_6) δ 8.16 (m, 1H), 7.64 (m, 2H), 7.17 (m, 1H), 6.84 (m, 1H), 6.77 (m, 1H), 4.29 (m, 2H), 4.15 (m, 1H), 4.03 (m, 1H), 3.77 (s, 3H), 3.52 (m, 3H), 3.04 (m, 2H), 2.78 (m, 1H), 2.70 (m, 2H), 1.81 (m, 1H), 1.61 (m, 1H). MS (DCI/NH_3) *m/e* 482$(M + H)^+$. Anal. ($C_{25}H_{25}ClN_3O_3S\cdot HCl\cdot 0.5H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-9-methoxy[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (40). 4-Methoxy-3-amino-2-carboethoxybenzothiophene[29] (0.80 g, 3.18 mmol), prepared from 2-methoxy-6-chlorobenzonitrile and ethyl thioglycolate, was reacted with the amine **15** (0.71 g, 2.88 mmol) according to method B to yield **40** (0.13 g, 10%) as a white solid, mp 193−195 °C; $[\alpha]_D$ +31.4° (*c* = 0.56, MeOH). ^{1}H NMR (MeOD) δ 1.65 (m, 2H), 2.02 (m, 2H), 2.60 (m, 2H), 2.92 (m, 2H), 3.18 (m, 1H), 3.62 (m, 3H), 3.85 (s, 3H), 4.15 (s, 3H), 4.45 (m, 2H), 6.80 (m, 2H), 7.08 (m, 1H), 7.20 (m, 1H), 7.60 (m, 2H). MS (DCI/NH_3) *m/e* 478 $(M + H)^+$. Anal. ($C_{26}H_{28}ClN_3O_4S\cdot HCl\cdot 1.5H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-9-cyano[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (41). 2,3-Dicyanonitrobenzene (2.6 g, 15 mmol) was treated with methyl thioglycolate (1.59 g, 15 mmol) and Na_2CO_3 (1.59 g, 15 mmol) in MeOH as described in **29** to yield 1.63 g of 3-amino-2-carbomethoxy-4-cyanobenzothiophene (47%), mp 169−170 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 6.66 (bs, 2H), 7.68 (t, *J* = 8 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H), 8.30 (d, *J* = 8 Hz, 1H). MS (DCI/NH_3) *m/e* 250 $(M + NH_4)^+$.

3-amino-2-carbomethoxy-4-cyanobenzothiophene (0.35 g, 1.5 mmol) and the amine **15** (0.37 g, 1.6 mmol) were treated by method B to yield **41** (0.360 g, 47%), mp 306−308 °C. ^{1}H NMR (DMSO-d_6) δ 1.52−1.68 (m, 1H), 1.70−1.85 (m, 1H), 2.33−2.58 (m, 1H), 2.62−2.92 (m, 3H), 2.95−3.08 (m, 1H), 3.44−3.60 (m, 3H), 3.77 (s, 3H), 3.94−4.17 (m, 2H), 4.19−4.35 (m, 2H), 6.73 (d, 1H), 6.84 (d, 1H), 7.17 (t, 1H), 7.82 (t, 1H), 8.18 (d, 1H), 8.55 (d 1H). MS (DCI/NH_3) *m/e* 473 $(M + H)^+$. Anal. ($C_{26}H_{24}N_4O_3S\cdot HCl\cdot 0.25 H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-9-methyl[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (42). 4-Methyl-3-amino-2-caroboethoxybenzothiophene was prepared by the method of Beck[20] from 6-nitro-*o*-tolunitrile and ethyl thioglycolate. The resulting benzothiophene (0.505 g, 2.15 mmol) and the amine 15 (0.45 g, 1.65 mmol) were treated by method B to yield **42** (0.525 g, 64%) as a white solid, mp >270 °C. ^{1}H NMR (DMSO-d_6) δ 7.94 (d, 1H, *J* = 8.1 Hz), 7.51 (dd,

1H, J = 8.1, 7.4 Hz), 7.30 (d, 1H, J = 0.0 Hz), 7.17 (dd, 1H, J = 8.1, 7.7 Hz), 6.84 (d, 1H, J = 8.5 Hz), 6.77 (m, 1H), 4.27 (m, 2H), 4.18 (m, 1H), 4.05 (m, 1H), 3.77 (s, 3H), 3.52 (m, 3H), 3.08 (m, 2H), 2.87 (s, 3H), 2.72 (m, 2H), 2.42 (m, 1H), 1.83 (m, 1H), 1.59 (m, 1H). MS (DCI/NH_3) *m/e* 462 $(M + H)^+$. Anal. ($C_{26}H_{28}ClN_3O_3S \cdot HCl \cdot 0.5H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-6-chloro[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (43). A solution of 2,3-dichlorobenzoic acid (10.0 g, 52.4 mmol) and oxalyl chloride (7.0 g, 55 mmol) in 100 mL of toluene was heated to reflux for 4 h, cooled, and concentrated. The resulting acid chloride was added to a mix of EtOAc and 12 N ammonium hydroxide and stirred vigorously. The layers were separated and the EtOAc layer was washed with 1 M HCl and brine, dried ($MgSO_4$), and concentrated to give 9.4 g of 2,3-dichlorobenzamide. ^{1}H NMR ($CDCl_3$) δ 6.06 (bs, 2H), 7.28 (t, J = 8 Hz, 1H), 7.54−7.62 (m, 2H). MS (DCI/NH_3) *m/e* 207 $(M + NH_4)^+$.

2,3-Dichlorobenzamide (9.4 g, 50 mmol) in $POCl_3$ (150 mL) was heated for 2 h at 95 °C. The solution was cooled and concentrated. The residue was partitioned between EtOAc and 10% aqueous K_2CO_3. The layers were separated, the EtOAc layer was washed with water (2 × 50 mL) and brine, dried ($MgSO_4$), and concentrated to yield 8.2 g of 2,3-dichlorobenzonitrile, mp 60−61 °C. ^{1}H NMR ($CDCl_3$) δ 7.34 (t, J = 8 Hz, 1H), 7.62 (dd, J = 8.1 Hz, 1H), 7.71 (dd, J = 8.1 Hz, 1H).

2,3-Dichlorobenzonitrile (1.7 g, 10 mmol) was treated with methyl thioglycolate and sodium carbonate in MeOH as described for example **29** to give, after chromatography (4:1 hexane/EtOAc), 0.29 g (12%) of 3-amino-2-carbomethoxy-7-chloro-benzothiophene. ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 5.90 (bs, 2H), 7.34 (t, J = 8 Hz, 1H), 7.48 (dd, J = 8.1 Hz, 1H), 7.56 (dd, J = 8,1 Hz, 1H). MS (DCI/NH_3) *m/e* 259 $(M + NH_4)^+$.

3-Amino-2-carbomethoxy-7-chloro-benzothiophene (0.30 g, 1.25 mmol) and the amine **15** (0.27 g, 1.1 mmol)) were treated by method B to yield **43** as a white solid (0.32 g, 55%), mp 250−253 °C. ^{1}H NMR (DMSO-d_6) δ 1.52−1.68 (m, 1H), 1.70−1.85 (m, 1H), 2.33−2.58 (m, 1H), 2.62−2.86 (m, 3H), 2.95−3.08 (m, 1H), 3.44−3.60 (m, 3H), 3.77 (s, 3H), 3.94−4.20 (m, 2H), 4.20−4.35 (m, 2H), 6.73 (d, 1H), 6.84 (d, 1H), 7.17 (t, 1H), 7.63 (t, 1H), 7.81 (d, 1H), 8.42 (d, 1H), 10.82 (s, 1H), 12.81 (s, 1H). MS (DCI/NH_3) *m/e* 482 $(M + H)^+$. Anal. ($C_{25}H_{24}ClN_3O_3S \cdot HCl \cdot 0.75\ H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-6-cyano[1]benzothieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (44). 2-Chloro-1,3-dicyanobenzene (0.972 g, 6.0 mmol) was treated with methyl thioglycolate and Na_2CO_3 in MeOH as described for example **29** to give 3-amino-2-carbomethoxy-7-cyano-benzothiophene (65%). ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 7.38 (bs, 2H), 7.62 (t, J = 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 8.50 (d, J = 8 Hz, 1H). MS (DCI/NH_3) *m/e* 250 $(M + NH_4)^+$.

The intermediate benzothiophene (0.35 g, 1.5 mmol) and the amine **15** (0.37 g, 1.5 mmol) were treated using method B to yield **44** (0.54 g, 68%), mp 265−269 °C. ^{1}H NMR (DMSO-d_6) δ 1.52−1.68 (m, 1H), 1.70−1.85 (m, 1H), 2.33−2.58 (m, 1H), 2.62−2.92 (m, 3H), 2.95−3.08 (m, 1H), 3.44−3.60 (m, 3H), 3.77 (s, 3H), 3.94−4.20 (m, 2H), 4.20−4.35 (m, 2H), 6.73 (d, 1H), 6.84 (d, 1H), 7.17 (t, 1H), 7.82 (t, 1H), 8.27 (d, 1H), 8.74 (d 1H) 10.55 (bs, 1H), 12.95 (s, 1H). MS (DCI/NH_3) *m/e* 473 $(M + H)^+$. Anal. ($C_{26}H_{24}N_4O_3S \cdot HCl \cdot H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-pyrido[3′,2′:4,5]thieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (45). 3-Amino-2-carbomethoxythieno[2,3-*b*]pyridine[21] (1.01 g, 3.6 mmol) and the amine **15** (0.75 g, 3.0 mmol) were treated by method B to yield **45** (0.68 g, 47%) as a white solid, mp 231 °C (dec). ^{1}H NMR (DMSO-d_6) δ 12.83 (m, 1H), 10.46 (br s, 1H), 8.82 (m, 2H), 7.67 (m, 1H), 7.17 (t, 1H, J = 7.9 Hz), 6.80 (m, 2H), 4.29 (m, 3H), 4.16 (m, 1H), 4.03 (m, 1H), 3.78 (s, 3H), 3.53 (m, 2H), 3.04 (m, 2H), 2.70 (m, 2H), 2.44 (m, 1H), 1.80 (m, 1H), 1.63 (m, 1H). MS (DCI/NH_3) *m/e* 449 $(M + H)^+$. Anal. ($C_{24}H_{24}N_4O_3S \cdot HCl \cdot 0.5H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-pyrido[4′,3′:4,5]thieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Dihydrochloride (46). A solution of 3-amino-2-carbomethoxythieno[2,3-c]pyridine[21] (0.61 g, 2.9 mmol) and Et_3N (0.88 mL, 6.3 mmol) in anhydrous CH_2Cl_2 under N_2 at −78 °C was treated with phosgene (1.5 mL of a 1.93 M solution in toluene, 2.9 mmol), and the reaction stirred at −78 °C for 45 min and room temperature for 1.5 h. Then the amine **15** (0.60 g, 2.4 mmol) in CH_2Cl_2 was added, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was partitioned between 1 M NaOH and CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue obtained was taken up in THF and treated with 3.6 mL of 1 M KOtBu in THF. The reaction mixture was stirred at room temperature for 1 h, then concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with 10% EtOH in CH_2Cl_2 saturated with NH_3 to provide after conversion to the HCl salt, **46** (1.01 g, 92%) (EtOH−Et_2O), mp 226−229 °C. ^{1}H NMR ($CDCl_3$) (free base) δ 1.48−1.62 (m, 1H), 1.70−1.83 (m, 1H), 2.45 (d, 3H), 2.52−2.75 (m, 3H), 2.88−2.99 (m, 1H), 3.03−3.13 (m, 1H), 3.40−3.63 (m, 3H), 3.78 (s, 3H), 4.31−4.47 (m, 2H), 6.64 (d, 1H), 6.69 (d, 1H), 7.03 (t, 1H), 8.01 (d, 1H), 8.60 (d, 1H), 9.19 (s, 1H). MS (DCI/NH_3) *m/e* 449 $(M + H)^+$. Anal. ($C_{24}H_{24}N_4O_3S \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-pyrido[2′,3′:4,5]thieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Dihydrochloride (47). Following the procedure described for example **46**, 3-amino-2-carbomethoxythieno[3,2-*b*]pyridine[21] (0.51 g, 2.4 mmol), Et_3N (0.74 mL, 5.3 mmol), phosgene (1.3 mL of 1.93 M solution in toluene, 2.4 mmol), and the amine **15** (0.50 g, 2.0 mmol) yielded 0.68 g (75%) of **47** which was converted to the HCl salt, mp 256−257 °C. ^{1}H NMR (DMSO-d_6) δ 1.53−1.68 (m, 1H), 1.73−1.86 (m, 1H), 2.60−3.10 (m, 4H), 3.64−3.83 (m, 4H), 3.77 (s, 3H), 3.83−4.35 (m, 4H), 6.73−6.87 (m, 2H), 7.17 (t, 1H), 7.65−7.71 (m, 1H), 8.66−8.70 (m, 1H), 8.84−8.88 (m, 1H), 10.30 and 10.64 (bs and bs, 1H), 12.79 (s, 1H). MS (DCI/NH_3) *m/e* 449 $(M + H)^+$. Anal. ($C_{24}H_{24}N_4O_3S \cdot 2HCl$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-pyrido[3′,4′:4,5]thieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Dihydrochloride (48). Following the procedure described for example 46 and using THF in place of CH_2Cl_2 as the solvent, 3-amino-2-carbomethoxythieno[3,2-*c*]pyridine[21] (0.51 g, 2.4 mmol), Et_3N (0.74 mL, 5.3 mmol), phosgene (1.3 mL of 1.93 M solution in toluene, 2.4 mmol), and the amine **15** (0.50 g, 2.0 mmol) provided 0.68 g (75%) of **48**, mp 261−262 °C. ^{1}H NMR ($CDCl_3$) (free base) δ 1.48−1.63 (m, 1H), 1.70−1.83 (m, 1H), 2.44−2.76 (m, 5H), 2.93−3.05 (m, 1H), 3.09−3.21 (m, 1H), 3.41−3.55 (m, 1H), 3.59−3.71 (m, 2H), 3.79 (s, 3H), 4.29−4.45 (m, 2H), 6.62 (d, 1H), 6.70 (d, 1H), 7.01 (t, 1H), 7.76 (d, 1H), 8.62 (d, 1H), 9.45 (s, 1H). MS (DCI/NH_3) *m/e* 449 $(M + H)^+$. Anal. ($C_{24}H_{24}N_4O_3S \cdot 2HCl$) C, H, N.

3-[2-((3a*R*,9b*R*)- *cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-thieno[2,3-*d*:4,5-*d*]dipyrimidine-2,4(1*H*,3*H*)-dione (49). A solution of 2-chloro-3-cyanopyrimidine (5.60 g, 40.1 mmol)[30] in DMF (75 mL) was treated with ethyl thioglycolate (5.30 g, 44.2 mmol) and sodium ethoxide (3.00 g, 44.2 mmol) at room temperature. After 4 h the reaction mixture was diluted with water and extracted several times with $CHCl_3$. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. The residual red-brown oil was purified by column chromatography on silica gel eluting first with 2:1 hexane:EtOAc then with 1:1 hexane:EtOAc to yield 4.26 g (48%) of ethyl 3-aminothieno[2,3-*d*]pyrimidine-2-carboxylate as a yellow solid, mp 138−140 °C. ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H), 4.39 (q, 2H), 6.08 (br s, 2H), 9.05 (s, 1H), 9.17 (s, 1H). MS (DCI/NH_3) *m/e* 224 $(M + H)^+$, 241 $(M + NH_4)^+$.

Ethyl 3-aminothieno[2,3-*d*]pyrimidine-2-carboxylate (0.40 g, 1.79 mmol), the amine **15** (0.42 g, 1.70 mmol), and Et_3N (0.54 g, 5.37 mmol) were reacted by method B. Chromatography on silica gel, eluting with EtOAc:HCOOH:H_2O (9:1:1) yielded

0.360 g (43%) of **49** as its formic acid salt. It was converted to the HCl salt by treatment with an excess of methanolic HCl, mp 243−246 °C. ^{1}H NMR (DMSO-d_6) δ 1.45 (m, 1H), 1.63 (m, 1H), 2.10−2.34 (m, 2H), 2.36−2.78 (m, 5H), 3.12−3.38 (m, 3H), 3.74 (s, 3H), 4.03 (t, 2H), 6.73 (d, 1H), 7.08 (t, 1H), 9.24 (s, 1H), 9.52 (s, 1H). MS (DCI/NH_3) *m/e* 450 $(M + H)^+$. Anal. ($C_{23}H_{23}N_5OS\cdot 2HCl\cdot H_2O$) C, H, N.

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz-[*e*]isoindol-2-yl)ethyl]-thieno[3,2-*d*:4,5-*d*]dipyrimidine-2,4(1*H*,3*H*)-dione (50). 5-Bromo-4-cyanopyrimidine (2.10 g, 11.4 mmol)[31] was treated with ethyl thioglycolate (1.38 g, 11.5 mmol) and Na_2CO_3 (1.21 g, 11.4 mmol) in EtOH (36 mL) as described for example **49** to yield 1.10 g (43%) of ethyl 3-aminothieno[3,2-*d*]pyrimidine-2-carboxylate, mp 139−141 °C. ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H), 4.41 (q, 2H), 6.17 (br s, 2H), 9.19 (s, 1H), 9.20 (s, 1H). MS (DCI/NH_3) *m/e* 224 $(M + H)^+$, 241 $(M + NH_4)^+$.

Ethyl 3-aminothieno[3,2-*d*]pyrimidine-2-carboxylate (0.400 g, 1.79 mmol), the amine **15** (0.384 g, 1.56 mmol), and Et_3N (0.332 g, 3.28 mmol) were treated by method B. Chromatography on silica gel, eluting with EtOAc:HCOOH:H_2O (9:1:1) yielded **50** (0.399 g, 52%) as its formic acid salt. It was converted to the HCl salt by treatment with an excess of methanolic HCl to give a tan solid, mp 230−235 °C. ^{1}H NMR (DMSO-d_6) δ 1.64 (m, 1H), 1.80 (m, 1H), 2.25−2.90 (m, 3H), 3.02 (m, 1H), 3.26−3.60 (m, 3H), 3.61−4.19 (m, 3H), 3.77 (s, 3H), 4.30 (m, 2H), 6.74 (d, 1H), 6.84 (d, 1H), 7.18 (t, 1H), 9.40 (s, 1H), 9.78 (s, 1H), 12.93 (s, 1H). MS (FAB/high resolution) calcd *m/e* for $(M + H)^+$ $C_{23}H_{24}N_5O_3S$, 450.1600; obsd *m/e*, 450.1599. Anal. ($C_{23}H_{24}N_5O_3S\cdot 3HCl\cdot 1H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*- 6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-pyrazino[2′,3′:4,5]thieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (51). Ethyl 3-aminothieno[2,3-*b*]pyrazine-2-carboxylate (1.56 g, 6.99 mmol),[29] the amine **15** (1.71 g, 6.94 mmol), and Et_3N (1.48 g, 14.58 mmol) were treated by method B. Chromatography on silica gel, eluting with EtOAc: HCOOH: H_2O (9:1:1) yielded 2.51 g (73%) of **51** as the formic acid salt. It was converted to the HCl salt by treatment with an excess of methanolic HCl to give a tan solid, mp 293−295 °C. ^{1}H NMR (DMSO-d_6) δ 1.62 (m, 1H), 1.80 (m, 1H), 2.30−2.87 (m, 3H), 3.02 (m, 1H), 3.30−3.90 (m, 4H), 3.78 (s, 3H), 4.02 (m, 1H), 4.14 (m, 1H), 4.30 (m, 2H), 6.74 (d, 1H), 6.85 (d, 1H), 7.17 (t, 1H), 8.91 (d, 1H), 8.99 (d, 1H), 13.01 (s, 1H). MS (DCI/NH_3) *m/e* 450 $(M + H)^+$. Anal. ($C_{23}H_{25}N_5O_3S\cdot 2HCl$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-chloro-pyrido[2′,3′:4,5]-thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Dihydrochloride (52). To a solution of 3-chloro-2-cyanopyridine (40 g, 0.29 mol) in acetic acid (500 mL) was added dropwise 30% hydrogen peroxide (52 g, 0.45 mol). After being stirred at 90 °C for 18 h, the reaction was cooled to 25 °C and a solution of Na_2SO_3 (57 g, 0.45 mol) in H_2O was added dropwise. The reaction was concentrated in vacuo to remove the bulk of the acetic acid, and the residue was partitioned between 1 M NaOH and CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, concentrated, and recrystallized from EtOAc to yield 23 g (51%) of 3-chloro-2-cyanopyridine-*N*-oxide. To the solution of the resulting pyridine *N*-oxide (12.2 g, 79 mmol) in DMF (160 mL) at 0 °C was added methyl thioglycolate (7.1 mL, 79 mmol), followed by the portionwise addition of sodium methoxide (8.5 g, 160 mmol). The reaction mixture was stirred at room temperature for 1 h and then it was poured onto ice, and the resulting solid was collected by filtration, washed with water, dissolved in CH_2Cl_2, dried ($MgSO_4$), filtered, concentrated, and recrystallized from EtOAc to yield 10.6 g (60%) of 3-amino-2-carbomethoxythieno[3,2-*b*]pyridine-4-oxide. The resulting thienopyridine-*N*-oxide (10.6 g, 47 mmol) was mixed with $POCl_3$ (100 mL). The reaction mixture was heated to 80 °C for 30 min, then concentrated and partitioned between CH_2Cl_2 and $NaHCO_3$ solution. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel (5:1 hexane: EtOAc) to yield 8.3 g (73%) of 3-amino-2-carbomethoxy-5-chlorothieno[3,2-*b*]pyridine and 2.0 g (18%) of the 3-amino-2-carbomethoxy-7-chlorothieno[3,2-*b*]pyridine. ^{1}H NMR ($CDCl_3$(5-chloro)) δ 3.92 (s, 3H), 6.15 (bs, 2H), 7.37 (d, 1H), 7.99 (d, 1H). MS (DCI/NH_3) *m/e* 243 $(M + H)^+$. ^{1}H NMR ($CDCl_3$(7-chloro)) δ 3.93 (s, 3H), 6.20 (bs, 2H), 7.41 (d, 1H), 8.54 (db, 1H), MS (DCI/NH_3) *m/e* 243 $(M + H)^+$.

3-Amino-2-carbomethoxy-5-chlorothieno[3,2-*b*]pyridine (540 mg, 2.2 mmol), prepared as described above, Et_3N (0.74 mL, 5.3 mmol), phosgene (1.2 mL of 1.93 M solution in toluene), and the amine **15** (0.50 g, 2.0 mmol) were reacted as described in **46** to provide 0.61 g (62%) of **52** which was converted to the HCl salt, mp 129−131°. ^{1}H NMR ($CDCl_3$) (free base) δ 1.59−1.74 (m, 1H), 1.89−2.01 (m, 1H), 2.52−2.65 (m, 1H), 2.73−2.91 (m, 3H), 2.91−3.05 (m, 1H), 3.32−3.53 (m, 1H), 3.73−3.88 (m, 1H), 3.82 (s, 3H), 3.88−4.13 (m, 1H), 4.26−4.39 (m, 1H), 4.51−4.66 (m, 1H), 4.66−4.86 (m, 2H), 6.69 (d, 1H), 6.78 (d, 1H), 7.10 (t, 1H), 7.36 (d, 1H), 7.87 (d, 1H). MS (DCI/NH_3) *m/e* 483 $(M + H)^+$. Anal. ($C_{24}H_{23}ClN_4O_3S\cdot HCl\cdot 0.25H_2O$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-methoxy-pyrido[2′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Dihydrochloride (53). A solution of 3-amino-2-carbomethoxy-5-chlorothieno[3,2-*b*]pyridine, prepared as described in **52** (5 g, 21 mmol), and sodium methoxide (4.5 g, 82 mmol) in MeOH (150 mL) was heated to reflux for 18 h. The reaction was concentrated and partitioned between EtOAc and $NaHCO_3$ solution. The EtOAc layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel (5:1 hex:EtOAc) to yield 2.5 g of the 3-amino-2-carbomethoxy-5-methoxythieno-[3,2-*b*]pyridine. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.02 (s, 3H), 6.05 (bs, 2H), 6.89 (d, 1H), 7.88 (d, 1H). MS (DCI/NH_3) *m/e* 239 $(M + H)^+$.

Following the procedure described for example **46**, 3-amino-2-carbomethoxy-5-methoxythieno[3,2-*b*]pyridine (530 mg, 2.2 mmol), Et_3N (0.71 mL, 5.1 mmol), phosgene (1.2 mL of 1.93 M solution in toluene), and the amine **15** (0.50 g, 2.0 mmol) provided 0.91 g (94%) of **53** which was converted to the HCl salt, mp 128−130°. ^{1}H NMR ($CDCl_3$ (free base)) δ 1.46−1.59 (m, 1H), 1.69−1.81 (m, 1H), 2.24−2.34 (m, 2H), 2.48−2.60 (m, 2H), 2.64−2.94 (m, 3H), 3.36−3.52 (m, 3H), 3.80 (s, 3H), 4.04 (s, 3H), 4.26 (t, 2H), 6.67 (d, 1H), 6.75 (d, 1H), 6.98 (d, 1H), 7.09 (t, 1H), 8.02 (d, 1H). MS (DCI/NH_3) *m/e* 479 $(M + H)^+$. Anal. ($C_{25}H_{26}N_4O_4S\cdot HCl$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-6-chloro-pyrido[2′,3′:4,5]-thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Dihydrochloride (54). From 3-amino-2-carbomethoxy-7-chlorothieno[3,2-*b*]pyridine, prepared as described for example **52** (0.540 g, 2.2 mmol), Et_3N (0.71 mL, 5.1 mmol), phosgene (1.2 mL of 1.93 M solution in toluene), and the amine **15** (0.50 g, 2.0 mmol) were reacted by the method described for example **46** to provide 0.46 g (43%) of **54**, mp >255 °C. ^{1}H NMR ($CDCl_3$) (free base) δ 1.54−1.70 (m, 1H), 1.84−1.96 (m, 1H), 2.48−2.61 (m, 1H), 2.65−2.92 (m, 4H), 3.35−3.50 (m, 1H), 3.70−3.87 (m, 2H), 3.80 (s, 3H), 4.31−4.42 (m, 1H), 4.45−4.63 (m, 3H), 6.68 (d, 1H), 6.77 (d, 1H), 7.10 (t, 1H), 7.42 (d, 1H), 8.58 (bd, 1H). MS (DCI/NH_3) *m/e* 483 $(M + H)^+$. Anal. ($C_{24}H_{23}ClN_4O_3S\cdot HCl$) C, H, N.

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-6-methoxy-pyrido[2′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Dihydrochloride (55). Following the procedure described for **53**, 3-amino-2-carbomethoxy-7-chlorothieno[3,2-*b*]pyridine (2.0 g, 8.2 mmol) provided 1.1 g (56%) of 3-amino-2-carbomethoxy-7-methoxythieno[3,2-b]pyridine. ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 4.05 (s, 3H), 6.18 (bs, 2H), 6.81 (d, 2H), 8.52 (d, 2H). MS (DCI/NH_3) *m/e* 239 $(M + H)^+$.

3-Amino-2-carbomethoxy-7-methoxythieno[3,2-b]pyridine (0.530 g, 2.2 mmol), Et_3N (0.71 mL, 5.1 mmol), phosgene (1.2 mL of 1.93 M solution in toluene), and the amine **15** (0.50 g, 2.0 mmol) were reacted for example **46** to yield 0.82 g (85%) of **55**, mp 235−237°. ^{1}H NMR ($CDCl_3$)(free base) δ 1.48−1.62 (m, 1H), 1.75−1.87 (m, 1H), 2.31−2.41 (m, 2H), 2.47−2.59 (m, 1H), 2.66−2.79 (m, 2H), 3.07−3.19 (m, 2H), 3.34−3.45 (m, 1H), 3.66 (q, 1H), 3.80 (s, 3H), 4.07 (s, 3H), 4.13 (q, 2H), 4.26−4.45

(m, 2H), 6.66 (d, 1H), 6.77 (d, 1H), 6.84 (d, 1H), 7.08 (t, 1H), 8.59 (d, 1H). MS (DCI/NH_3) *m/e* 479 $(M + H)^+$. Anal. ($C_{25}H_{26}N_4O_4S \cdot HCl \cdot 0.5H_2O$) C, H, N.

3-[2-(*cis*-(3a*R*,9b*R*)-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-7-methyl-pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (56). 3-Carboxamido-2-hydroxy-6-methylpyrazine[32] (4.09 g, 26.70 mmol), was suspended in Et_3N (5.41 g, 53.41 mmol), cooled to 0° and reacted with 70 mL $POCl_3$. The mixture was heated to reflux for 3 h and concentrated in vacuo. The resulting black oil was extracted with ether (5 × 100 mL), and the combined extracts were treated with 10% Na_2CO_3 (250 mL). The organic layers were separated, washed with water and brine, dried (Na_2SO_4), and concentrated to yield 3-cyano-2-chloro-6-methyl-pyrazine (3.16 g, 77%) as a fluffy yellow solid, mp 63−65 °C. ^1H NMR ($CDCl_3$) δ 2.70 (s, 3H), 8.50 (s, 1H). MS (DCI/NH_3) *m/e* 171 $(M + NH_4)^+$.

3-Cyano-2-chloro-6-methylpyrazine (1.00 g, 6.51 mmol) was treated as described for example **49** with ethyl thioglycolate (0.782 g, 6.51 mmol) and Na_2CO_3 (0.69 g, 6.51 mmol) to yield ethyl-3-amino-6-methyl-thieno[2,3-*b*]pyrazine-2-carboxylate (1.12 g, 72%) as a bright yellow solid, mp 121−123 °C (EtOH/H_2O). ^1H NMR ($CDCl_3$) δ 1.41 (t, 3H), 2.71 (s, 3H), 4.38 (q, 2H), 6.15 (br s, 2H), 8.45 (s, 1H). MS (DCI/NH_3) *m/e* 238 $(M + H)^+$, 255 $(M + NH_4)^+$. Anal. calcd for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; Found: C, 50.75; H, 4.45; N, 17.70.

The intermediate ethyl-3-amino-6-methyl-thieno[2,3-*b*]pyrazine-2-carboxylate (0.275 g, 1.16 mmol), Et_3N (0.23 g, 2.28 mmol), and the amine **15** (0.280 g, 1.14 mmol) were treated by method B. Chromatography of the crude concentrate on silica gel, eluting with EtOAc:HCOOH:H_2O (18:1:1), provided the formate salt of the product. Conversion to the HCl salt afforded **56** (0.281 g, 49%) as a tan solid, mp 264−265 °C. ^1H NMR (DMSO-d_6) δ 1.61 (m,1H), 1.80 (m, 1H), 2.37−2.83 (m, 3H), 2.73 (s, 3H), 3.03 (m, 1H), 3.44−3.63 (m, 4H), 3.77 (s, 3H), 4.02 (m, 1H), 4.13 (m, 1H), 4.28 (m, 2H), 6.74 (d, 1H), 6.84 (d, 1H), 7.17 (t, 1H), 8.88 (s, 1H), 12.95 (s, 1H). MS (DCI/NH_3) *m/e* 464 $(M + H)^+$. Anal. ($C_{24}H_{25}N_5O_3S \cdot HCl \cdot 1.50H_2O$) C, H, N.

3-[2-(*cis*-(3a*R*,9b*R*)-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-7,8-dimethylpyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (57). 5,6-Dimethyl-2-hydroxy-3-carboximidopyrazine[33] (4.4 g, 26.3 mmol) was treated with $POCl_3$ (70 mL), and Et_3N (7.3 mL, 52.3 mmol) as described for example **56** to give 3.3 g (75%) of 2-chloro-3-cyano-5,6-dimethylpyrazine as a yellow solid, mp 83−85 °C. ^1H NMR (DMSO-d_6) δ 2.54 (s, 3H), 2.59 (s, 3H). MS (DCI/NH_3) *m/e* 185 $(M + H)^+$.

The intermediate dimethylpyrazine (1.5 g, 8.95 mmol), ethyl thioglycolate (1.08 mL, 9.85 mmol), and Na_2CO_3 (0.949 g, 8.95 mmol) were treated as described for example **49** to afford 1.3 g (58%) of ethyl 3-amino-5,6-dimethylthieno[2,3-*b*]pyrazine-2-carboxylate, mp 136−139 °C. ^1H NMR ($CDCl_3$) δ1.4 (t, 3H), 2.64 (s, 3H), 2.68 (s, 3H), 4.39 (q, 2H), 6.12 (br s 2H). MS (DCI/NH_3) *m/e* 252 $(M + H)^+$.

The intermediate thienopyrazine (0.269 g, 1.07 mmol), the amine **15**, and Et_3N (0.313 mL, 2.25 mmol) were treated by method B to yield 0.236 g of **57** as a tan solid, mp 308−310 °C. ^1H NMR (DMSO-d_6) δ 1.61 (s, 1H), 1.79 (m, 1H), 2.69 (s, 3H), 2.6−2.79 (m, 4H), 3.01 (m, 1H), 3.32 (s, 3H), 3.52 (m, 2H), 3.78 (s, 3H), 3.09−4.81 (sev m, 4H), 6.71−6.86 (m, 3H), 7.18 (m, 1H), 12.86 (m, 1H). HRMS calcd for $C_{25}H_{28}N_5SO_3$, 478.1913; found, 478.1913. Anal. ($C_{25}H_{27}N_5SO_3 \cdot HCl \cdot H_2O$) C, H, N.

3-[2-(*cis*-(3a*R*,9b*R*)-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (58). A mixture of 5- and 6-phenyl regioisomers of 2-hydroxy-3-carboxamidopyrazines **33** (7.2 g, 33.5 mmol) was treated with $POCl_3$ (56 mL, 586 mmol) and Et_3N (9.3 mL, 67 mmol) as in example 56 to give a white solid as a 40:60 mixture of the 2-chloro-3-cyano-5-phenylpyrazine and 2-chloro-3-cyano-6-phenylpyrazine, mp (mixture) 121−125 °C. ^1H NMR ($CDCl_3$) δ 7.52 (m, 5H major and minor), 8.02 (d, 2H (major)), 8.11 (d, 2H (minor)), 9.0 (s, 1H (major)), 9.05 (s, 1H (minor)). MS (DCI/NH_3) *m/e* 215 $(M + H)^+$.

The obtained mixture of 5- and 6-phenylpyrazines (1.55 g, 7.16 mmol) was treated with methyl thioglycolate (0.708 mL, 7.88 mmol) and $NaOCH_3$ (0.386 g, 7.16 mmol) in anhydrous DMF (2 mL) at room temperature for 1 h. The reaction mixture was partitioned between saturated NH_4Cl/CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel, eluting with CH_2Cl_2 to yield methyl 3-amino-5-phenylthieno[2,3-*b*]pyrazine-2-carboxylate (0.43 g, 21%) as a yellow solid. ^1H NMR ($CDCl_3$) δ 3.94 (s, 3H), 6.26 (bs, 2H), 7.53 (m, 3H), 8.09 (d, H) 2H), 9.09 (s, 1H). MS (DCI/NH_3) *m/e* 286 $(M + H)^+$. Further eluting yielded the isomeric methyl-3-amino-6-phenyl-thieno[2,3-*b*]-pyrazine-2-carboxylate (0.35 g, 17%) as a yellow-green solid. ^1H NMR ($CDCl_3$) δ 3.95 (s, 3H), 6.11 (br s, 2H), 7.55 (m, 3H), 8.12 (m, 2H), 9.03 (s, 1H). MS (DCI/NH_3) *m/e* 286 $(M + H)^+$.

Methyl 3-amino-5-phenylthieno[2,3-*b*]pyrazine-2-carboxylate (0.461 g, 1.62 mmol), the amine 15 and Et_3N (0.048 g, 3.40 mmol) were treated by method B to give 0.208 g (24%) of **58** as a green-yellow solid, mp 296−298 °C. ^1H NMR (DMSO-d_6) δ 1.6 (m, 1H), 1.8 (m, 1H), 2.65 (m, 2H), 3.02 (m, 1H), 3.52 (m, 3H), 3.78 (s, 3H), 4.02 (m, 2H), 4.3 (m, 2H), 6.72−6.86 (m, 2H), 7.27 (dd, 1H), 7.6 (m, 3H), 8.48 (d, 2H), 9.55 (s, 1H). MS (DCI/NH_3) *m/e* 526 $(M + H)^+$. Anal. ($C_{29}H_{28}N_5SO_3 \cdot HCl \cdot 0.5H_2O$) C, H, N.

3-[2-(*cis*-(3a*R*,9b*R*)-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-7-phenyl-pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (59). Methyl-3-amino-6-phenyl-thieno[2,3-*b*]pyrazine-2-carboxylate (0.675 g, 2.37 mmol) Et_3N (0.48 g, 4.74 mmol) and the amine **15** (0.550 g, 2.25 mmol) were treated by method B to yield 0.435 g (33%) of 59 as a yellow-green solid, mp 310−311 °C. ^1H NMR (DMSO-d_6) δ 1.63 (m, 1H), 1.80 (m, 1H), 2.35−2.90 (m, 3H), 3.04 (m, 1H), 3.44−3.65 (m, 4H), 3.78 (s, 3H), 4.03 (m, 1H), 4.15 (m, 1H), 4.30 (m, 2H), 6.75 (d, 1H), 6.84 (d, 1H), 7.17 (t, 1H), 7.61 (m, 3H), 8.33 (m, 2H), 9.59 (s, 1H), 13.03 (br s, 1H). MS (DCI/NH_3) *m/e* 526 $(M + H)^+$. Anal. ($C_{29}H_{27}N_5O_3S \cdot HCl$) C, H, N.

3-[2-(*cis*-(3a*R*,9b*R*)-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-chloro-pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (60). To a solution of 2-chloro-3-cyanopyrazine (5.00 g, 35.94 mmol) in concentrated H_2SO_4 (35 mL) that was cooled to 0 °C was added $K_2S_2O_8$ (11.65 g, 43.95 mmol) portionwise. The flask was fitted with a $CaCl_2$ drying tube, the reaction mixture was allowed to warm to room temperature and stirred for 24 h. After partitioning between $CHCl_3$ and ice water, the separated aqueous phase was extracted with $CHCl_3$. The combined organic layers were washed with water, saturated $NaHCO_3$, and brine, and dried ($MgSO_4$). Concentration gave 2.01 g (36%) of 2-chloro-3-cyano-pyrazino-4-oxide as an off-white solid. ^1H NMR ($CDCl_3$) δ 8.12 (d, 1H), 8.38 (d, 1H). MS (DCI/NH_3) *m/e* 173 $(M + NH_4)^+$.

2-Chloro-3-cyano-pyrazino-4-oxide (2.90 g, 18.64 mmol) was dissolved in DMF (100 mL) under nitrogen and treated with ethyl thioglycolate (2.24 g, 18.64 mmol). After cooling the solution to 0 °C, it was treated with solid NaOEt (2.54 g, 37.29 mmol), allowed to warm to room temperature, and then stirred for 13 h. The reaction mixture was partitioned between EtOAc and brine, and the layers were separated. After extracting the aqueous phase with EtOAc, the combined organic layers were washed with water and brine and dried ($MgSO_4$). Concentration gave a yellow solid that was purified by column chromatography on silica gel eluting with 2:1 then 1:1 hexane:EtOAc to yield ethyl-3-aminothieno[2,3-*b*]pyrazine-2-carboxylate-4-oxide (3.50 g, 78%) as a yellow solid, mp 126−127. ^1H NMR ($CDCl_3$) δ 1.40 (t, 3H), 4.38 (q, 2H), 7.25 (br s, 2H), 8.02 (d, 1H), 8.41 (d, 1H). MS (DCI/NH_3) *m/e* 240 $(M + H)^+$, 257 $(M + NH_4)^+$. Anal. ($C_9H_9N_3O_3S$) C, H, N.

The intermediate thienopyrazine *N*-oxide (0.88 g, 3.68 mmol) was dissolved in $POCl_3$ (50 mL) under nitrogen and heated to 95 °C for 3 h. The reaction mixture was concentrated and partitioned between EtOAc and water. After the aqueous

phase was extracted with EtOAc, the combined organic layers were washed with water, saturated $NaHCO_3$, and brine and dried over Na_2SO_4. Concentration gave a two component mixture that was separated by column chromatography on silica gel using a gradient elution from 10:1 to 1:1 hexanes: EtOAc to give ethyl-3-amino-5-chloro-thieno[2,3-*b*]pyrazine-2-carboxylate (0.56 g, 59%) and unreacted starting material (0.30 g, 34%). ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3H), 4.40 (q, 2H), 6.11 (br s, 2H), 8.60 (s, 1H). MS (DCI/NH_3) *m/e* 258 $(M + H)^+$, 275 $(M + NH_4)^+$.

Ethyl-3-amino-5-chloro-thieno[2,3-*b*]pyrazine-2-carboxylate (0.420 g, 1.63 mmol) was treated by method B with Et_3N (0.32 g, 3.20 mmol) and the amine **15** (0.394 g, 1.60 mmol) to yield **60** (0.394 g, 47%) as a yellow solid, mp 262−265 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 1.61 (m, 1H), 1.79 (m, 1H), 2.35−2.90 (m, 3H), 3.02 (m, 1H), 3.41−3.65 (m, 4H), 3.77 (s, 3H), 4.01 (m, 1H), 4.12 (m, 1H), 4.39 (m, 2H), 6.75 (d, 1H), 6.84 (d, 1H), 7.17 (t, 1H), 9.04 (s, 1H), 13.03 (br s, 1H). MS (DCI/NH_3) *m/e* 484 $(M + H)^+$. Anal. ($C_{23}H_{22}ClN_5O_3S$·HCl·$0.75H_2O$) C, H, N.

3-[2-(*cis*-(3a*R*,9b*R*)-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-2-yl)ethyl]-8-methoxy-pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Hydrochloride (61). Ethyl-3-amino-5-chloro-thieno[2,3-*b*]pyrazine-2-carboxylate (0.700 g, 2.72 mmol) was dissolved in 75 mL of MeOH and treated with solid NaOMe (1.47 g, 27.2 mmol), and the resulting solution was refluxed for 12 h. The reaction mixture was partitioned between saturated NH_4Cl and $CHCl_3$. After the aqueous phase with $CHCl_3$, the combined organics were washed with water then brine and dried (Na_2SO_4). Concentration gave 0.50 g (77%) pure ethyl-3-amino-5-methoxy-thieno[2,3-*b*]pyrazine-2-carboxylate as a yellow solid, mp 181−182 °C. ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 4.05 (s, 3H), 6.02 (br s, 2H), 8.30 (s, 1H). MS (DCI/NH_3) *m/e* 240 $(M + H)^+$, 257 $(M + NH_4)^+$. Anal. ($C_9H_9N_3O_3S$) C, H, N.

Ethyl-3-amino-5-methoxy-thieno[2,3-*b*]pyrazine-2-carboxylate (0.400 g, 1.67 mmol) was treated by method B with Et_3N (0.25 g, 2.50 mmol) and the amine **15** (0.411 g, 1.67 mmol) to yield 0.457 g (56%) of **61** as a tan solid, mp 243−245 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 1.63 (m, 1H), 1.80 (m, 1H), 2.42 (m, 1H), 2.58−2.86 (m, 2H), 3.02 (m, 1H), 3.37−3.91 (m, 4H), 3.79 (s, 3H), 3.91−4.20 (m, 2H), 4.10 (s, 3H), 4.30 (m, 2H), 6.75 (d, 1H), 6.84 (d, 1H), 7.17 (t, 1H), 8.56 (s, 1H), 12.77 (s, 1H). HRFAB calcd for $C_{24}H_{26}N_5O_4$, 480.1706; found, 480.1710. Anal. ($C_{24}H_{25}N_5O_4S$·HCl·$0.5H_2O$) C, H, N.

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