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

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In search of a uroselective α_{1A} subtype selective antagonist, a novel series of 6-OMe hexahydrobenz[*e*]isoindoles attached to a bicyclic heterocyclic moiety via a two-carbon linker was synthesized. It was found that in contrast to the previously described series of tricyclic heterocycles,[1] this bicyclic series has very specific requirements for the heterocyclic attachments. The most important structural features contributing to the α_{1A}/α_{1B} selectivity of these compounds were identified. In vitro functional assays for the α_1 adrenoceptor subtypes were used to further characterize the most selective compounds, and in vivo models of vascular vs prostatic tone were used to assess uroselectivity. Compound **48** showed the highest degree of selectivity in the radioligand binding assays (56-fold), in the in vitro functional tests (80-fold), and for in vivo prostate selectivity (960-fold).

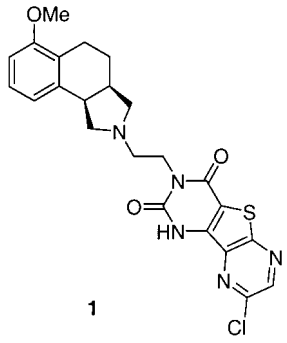
Introduction

Benign prostatic hyperplasia (BPH) is a highly prevalent condition, with the percentage incidence approximately equaling a man's age.[2] This condition is characterized by a collection of urological symptoms including hesitancy, nocturia, poor urine flow, frequency of urination, and sensations of urgency. It was demonstrated that the dynamic component of BPH is mediated primarily through prostatic α_1 adrenoceptors.[3] First-generation drugs used to treat BPH (i.e., terazosin,[4] doxazosin,[5] and alfuzosin[6]), although effective in improving symptoms of BPH, were found to be suboptimal because of the dose-limiting side effects. These included hypotension, dizziness, and muscle fatigue and were believed to be mediated by the blockade of α_1 receptors in the vasculature and the central nervous system.

Within the past decade the heterogeneity of the α_1 receptor was realized on both a molecular level and a pharmacological level.[7] It was shown that even though all three subtypes of the human α_1 receptor were present in the prostate, the α_{1A} receptor was the most prevalent.[8] There was also scientific evidence of a prominent role of α_{1B} receptor in the regulation of blood pressure.[9] This stimulated interest in finding a "uroselective" α_{1A}/α_{1B} selective agent that would have a better side effect profile. The therapeutic relevance of these findings has been proven in the clinical setting where tamsulosin, the second-generation drug for the treatment of BPH (20-fold selective for α_{1A} over α_{1B} receptors),[10] demonstrated a more favorable side effect profile.[11]

There has also been considerable interest in further understanding the role of α_{1D} receptor in the design of a "uroselective " drug. It was suggested that blockade of this receptor could ameliorate the irritative symptoms of BPH that result from the involuntary contractions of the bladder smooth muscle.[12] Thus, agents with improved selectivity for α_{1A}/α_{1B} receptor with activity at α_{1D} receptor could demonstrate further improvement in the side effect profile.

Chart 1



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A number of α_{1A} subtype selective antagonists representing different structural classes of compounds such as SNAP 5089 (dihydropyridine),[13] GG818 (oxazole),[14] dihydropyrimidinones,[15,16] and SNAP 7915 (oxazolidinone)[17] were disclosed recently. A review[18] on the development of α_{1A} antagonists outlined the progress made in this field within the past decade.

In our earlier publication[1] we described structure−activity (SAR) studies on a series of hexahydrobenz[*e*]-isoindoles attached to a tricyclic heterocycle, as in compound **1** (Chart 1). This compound exhibited a 50-fold selectivity for the α_{1A}/α_{1D} receptors versus α_{1B} receptor. Although the requirements for the left-hand portion of the molecule were found to be very specific (6-methoxybenz[*e*]isoindole with (R,R) stereochemistry of the ring junction, and a two-carbon chain linker) a

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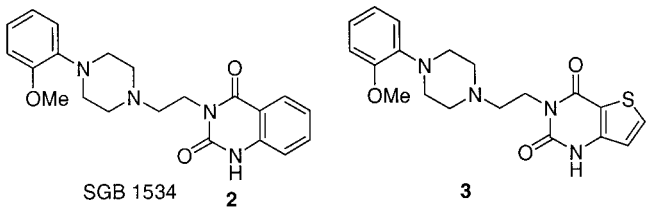
Chart 2



wide variety of tricyclic heterocyclic attachments were tolerated in the right-hand portion of the molecule with the retention of potency and selectivity. We were interested in finding out if the replacement of tricyclic heterocycles with the bicyclic units would result in improved selectivity and potency. Additional impetus to the bicyclic heterocyclic replacements was provided by the fact that there were known α_1 adrenergic antagonists **2** and **3** (Chart 2) with such structural elements.[19]

The initial attempt at appending a bicyclic heterocycle to the 6-OMe-benz[*e*]isoindole resulted in compound **4** (Chart 3). Unfortunately, although this compound retained α_1 potency, it was not subtype-selective. Previously, we found that introduction of substituents, as well as other heteroatoms, augmented potency and selectivity. Consequently, we initiated further study of this class of compounds.

Chemistry

SAR studies of the parent structure focused on identification of the optimal bicyclic heterocyclic attachment. The synthesis of target structures was accomplished via two different methods. In method A (Scheme 1) quinazolinediones **10** were formed by the coupling of isocyanate intermediates **8** with the primary amines **6**[1] followed by cyclization accomplished thermally or assisted by potassium *tert*-butoxide. The isocyanates **8** were obtained from the corresponding aminoesters **7** by treatment with triphosgene in toluene at reflux. In certain cases the isocyanates were not isolated but formed in situ using phosgene solution in toluene in the presence of triethylamine and then reacted directly with the primary amines **6**. The primary amines **6** or **6a** were derived from the benz[*e*]isoindoles **5** or **5a**[1] via alkylation with chloroacetonitrile followed by reduction of the resulting nitriles with lithium aluminum hydride. Method B (Scheme 1) entailed the reaction of 2-chloroethyl isocyanate[20] with the starting aminoesters **7** to give the haloalkyl ureas **9** that were in turn reacted with the benz[*e*]isoindoles **5**.

The majority of monosubstituted anthranilic acids used in this study were obtained from commercial sources. Disubstituted anthranilic acids that were not available commercially were most conveniently prepared via oxidative cleavage of substituted isatins.[21] Aminocarboethoxythiophenes were obtained from commercial sources or synthesized via known methods.[22,23] Aminocarboethoxypyridines used in this study were prepared in accordance with literature procedures.[24,25]

Synthesis of 1-methyl-substituted quinazolinedione **46** is outlined in Scheme 2. Methyl 2-amino-4,5-dimethoxybenzoate was converted to the intermediate methyl 4,5-dimethoxy-2-(methylamino)benzoate **44** by the two-step sequence.[26] Compound **44** was reacted with chloroethylisocyanate to yield the intermediate chloroethylquinazolinedione **45** that was in turn reacted with the benz[*e*]isoindole **5** to form the desired *N*-methyl-substituted derivative **46**.

The route to 4-quinazolinone compounds is depicted in Scheme 3. Ethyl 6-amino-3,4-dimethoxybenzoate was converted to the intermediate formamidine **47** that was coupled with **6** in the presence of *p*-toluenesulfonic acid to yield the 4-quinazolinone **48**. Dihydroquinazolinone **49** was obtained by the hydrogenation of compound **48**.

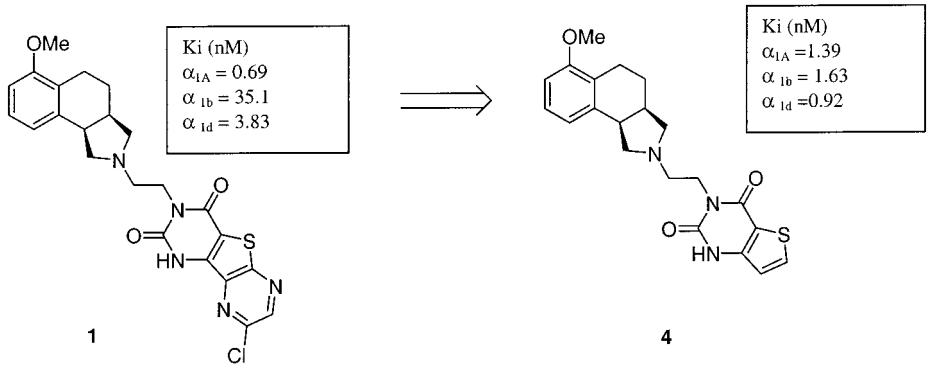
Scheme 4 illustrates the synthesis of tetrahydroquinazoline **52** and 2-quinazoline derivative **53**. The starting dimethoxynitrobenzaldehyde was coupled with the amine **6** to result in the intermediate nitro derivative **50** that was hydrogenated over Pd/C to yield the amine **51**. Reaction of formaldehyde with **51** produced compound **52,** whereas action of carbonyldiimidazole on **51** resulted in **53**. Scheme 5 outlines the synthesis of isoquinoline derivatives **55** and **56**. The starting benz[*e*]isoindole **5** was reacted with 1-bromo-2-chloroethane to result in chloroethyl derivative **54** that was coupled with the corresponding isoquinolines to yield **55** and **56**. Compound **57** was synthesized by the coupling of the 2-amino-4,5-dimethoxybenzoic acid with the amine **6**.

Results and Discussion

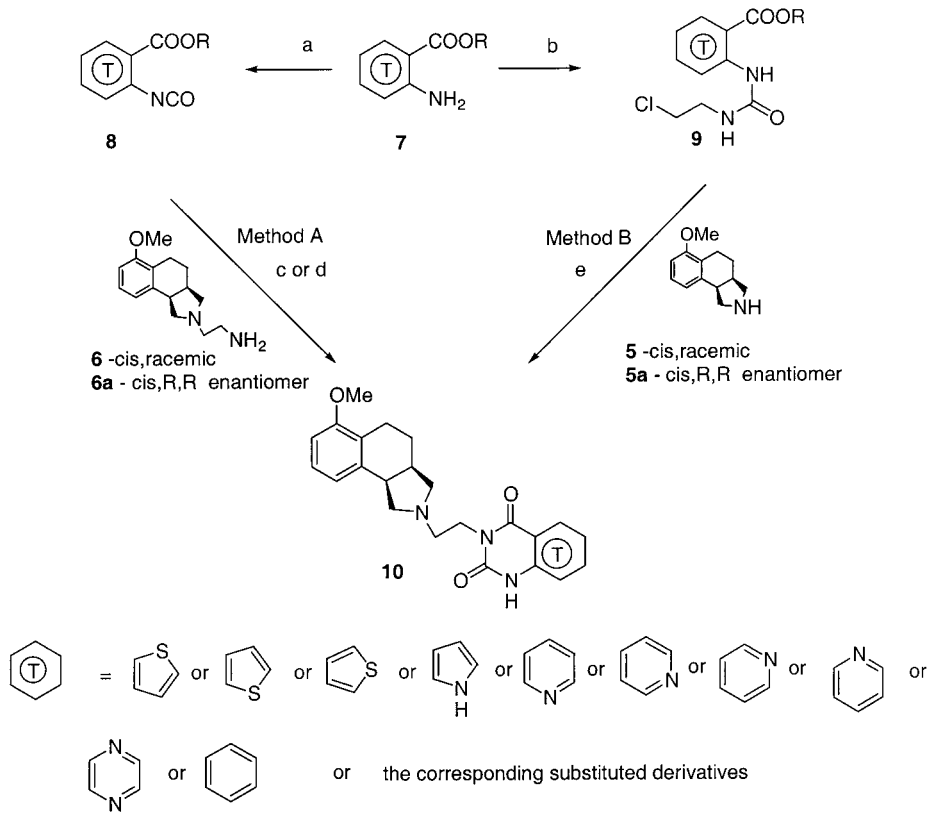
Compounds were assayed for their affinity at the α_1 receptor subtypes. The SAR study reported herein was broken into the following parts: (i) variation of the bicyclic heterocycles; (ii) effects of the substituents on the quinazolinedione portion of the molecule; (iii) modification of the pyrimidinedione ring.

The first objective of our studies was to investigate compounds that could be viewed as the truncated version of the tricyclic lead compound **1**. The results of this effort are summarized in Table 1. As is evident,

Chart 3

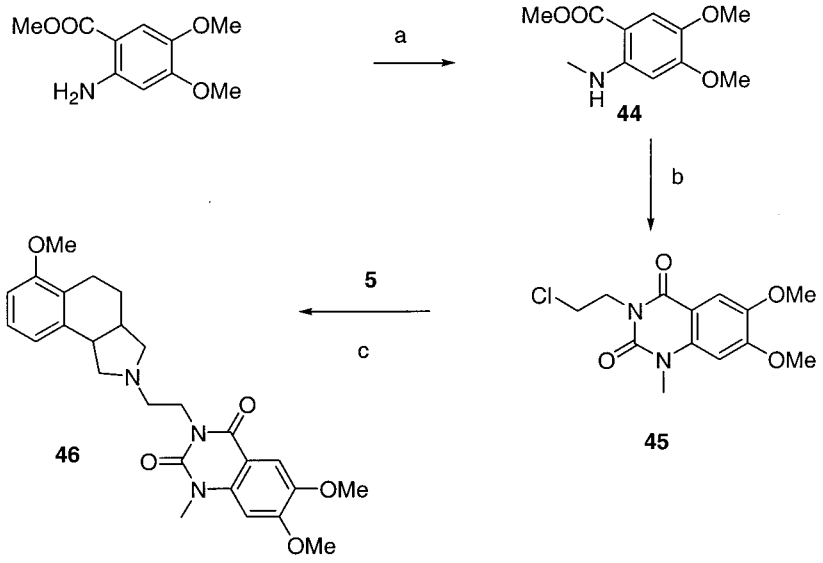


Scheme 1[a]



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

Scheme 2[a]

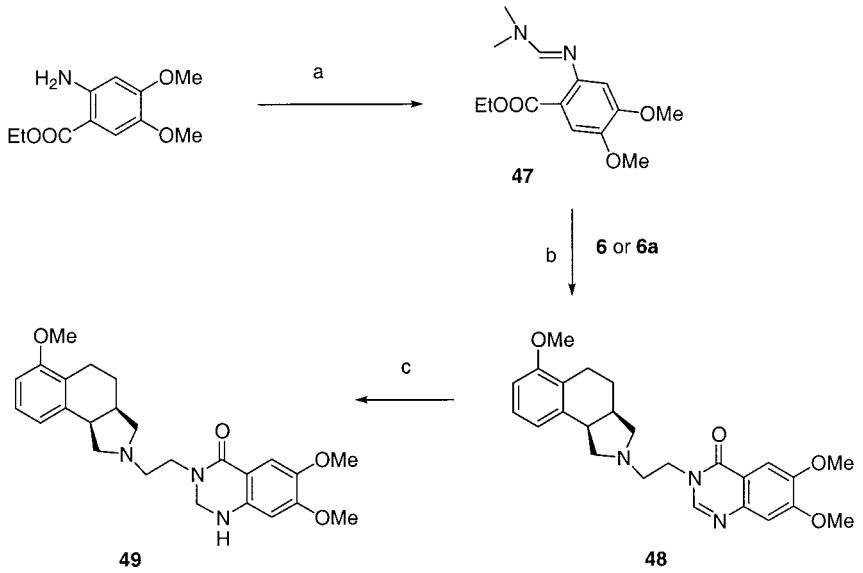


[a] Conditions and reagents: (a) (i) HCO_2H, acetic anhydride, THF, (ii) $BH_3(CH_3)_2S$, THF; (b) 2-chloroethylisocyanate, toluene; (c) diisopropylethylamine, CH_3CN.

with the exception of **15**, thieno[3,2-d]pyrimidinediones were generally not selective for the α_{1A} receptor. It is of interest to note the different effects of substituents on the thiophene ring. The 6-phenyl group, as in **14**, significantly lowered the potency, whereas the introduction of the phenyl group in the 7-position as in **13** resulted in increased affinity at the α_{1A} receptor but no improvement in selectivity. The smaller OMe group, as in compound **15**, increased both the potency and the selectivity. The combination of methoxy and alkyl group substitution as in **17** and **18** resulted in somewhat diminished selectivity by comparison with **15**.

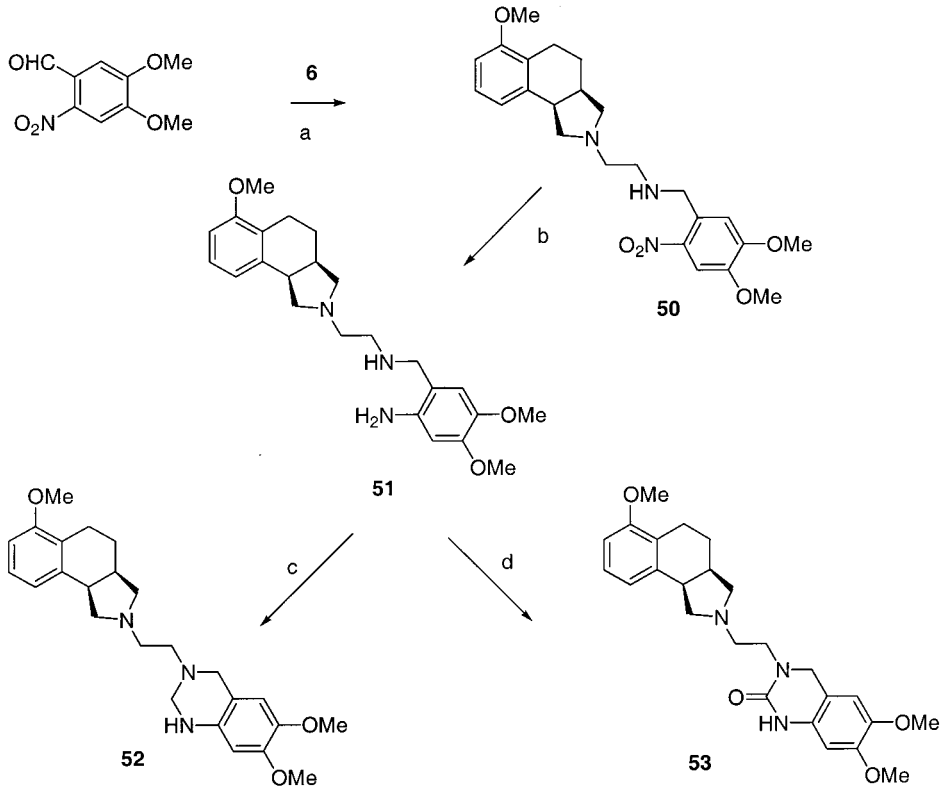
Further explorations of the effect of different heterocyclic isosteres on the selectivity and potency of bicyclic analogues are summarized in Table 2. It is evident that all these analogues lacked the desired level of selectivity. Of all the replacements, one of the more potent examples was the quinazolinedione **27**. The more detailed SAR study of the substituted quinazolinediones was made possible by the abundance of commercially

Scheme 3[a]



[a] Conditions and reagents: (a) $(Me)_2NCH(OMe)_2$, DMF; (b) *p*-toluenesulfonic acid, dioxane, reflux; (c) H_2, Pd/C.

Scheme 4[a]

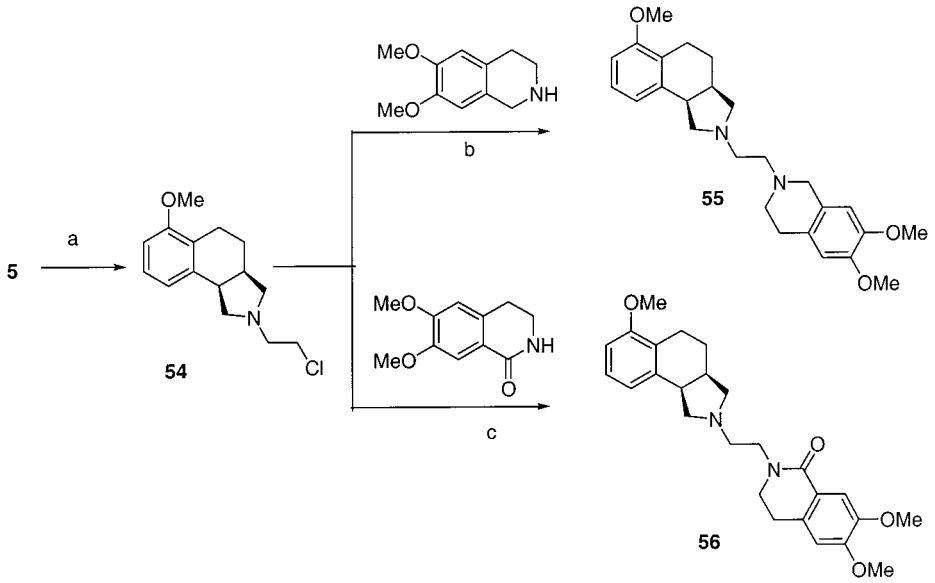


[a] Conditions and reagents: (a) $NaBH_4$, MeOH; (b) H_2, Pd/C, MeOH; (c) 37% HCHO, HCl, EtOH; (d) CDI, CH_3CN.

available anthranilic acids. The results of this SAR analysis are presented in Table 3. It is of interest to note that the 8-OMe-substituted derivative **28** manifested only marginal selectivity whereas 7-substituted derivatives, in particular 7-CN and 7-OCH_3 (**30** and **31**) showed somewhat improved selectivity and affinity for the α_{1A} receptor. It is noted that similar selectivities were observed in compounds **15** and **31**, wherein the thiophene ring was replaced by phenyl. The moderate selectivity of compound **31** was lost when the substituents were moved to the 5-position of the ring (**36** and **37**). The disubstituted derivatives, like the 6,7-dimethoxy (**40**), the 7,8-dimethyl (**42**), and the 7,8-dimethoxy (**43**), were generally more selective than their monosubstituted analogues.

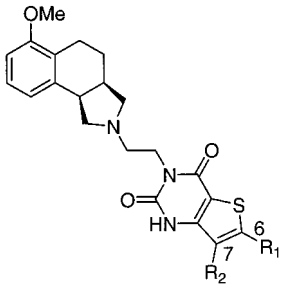
Since compound **40** represented the most selective compound so far, we explored pyrimidine ring modifications in the quinazolinedione series with 6,7-dimethoxy substitution (Table 4). Introduction of the methyl group as in compound **46** attenuated the selectivity. The removal of the 2-carbonyl group on the other hand improved the (α_{1A} vs α_{1B}) selectivity and resulted in the most selective compound in the series, compound **48**. Saturation of the double bond of **48** resulted in com-

Scheme 5[a]



[a] Conditions and reagents: (a) 1-bromo-2-chloroethane, K_2CO_3, DMF; (b) K_2CO_3, DMF; (c) NaH, DMF.

Table 1. SAR of Thieno[3,2-d] Pyrimidindiones



			radioligand binding K_i [f] (nM)			
compound	R_1	R_2	α_{1A}[b]	α_{1B}[b]	α_{1D}[b]	selectivity ratio[e]
11[a]	H	H	1.39 (1.21, 1.6)	1.63 (1.43, 1.85)	0.92 (0.89, 0.91)	1.17
12[a]	H	Me	0.85 (0.73, 0.98)	1.28 (1.04, 1.57)	0.71 (0.68, 0.71)	1.50
13[a]	H	Ph	0.33[c] (0.30, 0.35)	0.33[c] (0.25, 0.42)	0.66[c] (0.60, 0.72)	1.0
14[a]	Ph	H	7.73[d]	11.3[d]	4.40[d]	1.5
15	OMe	H	0.04 (0.02, 0.08)	0.74 (0.64, 0.86)	0.24 (0.20, 0.24)	18
16	COOMe	H	1.48 (1.06, 1.48)	3.37 (2.65, 4.29)	1.38 (1.06, 1.79)	2.3
17	OMe	Me	1.09[d]	7.14[d]	1.45[d]	6.5
18	OMe	i-propyl	0.41[d]	2.31[d]	1.5	5.6

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

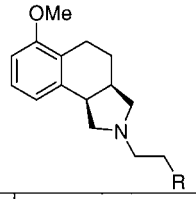
pound **49** with a drastically lowered potency. Elimination of both carbonyl groups as in **52** and **55** produced a further loss of affinity. It was also shown that the 4-carbonyl group was absolutely essential for the affinity at the receptors. Its removal as in **53** led to a dramatic loss of the potency.

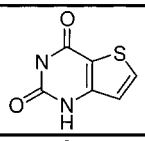
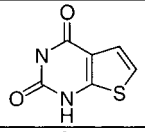
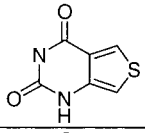
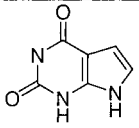
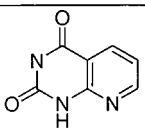
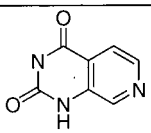
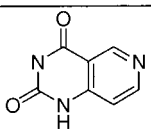
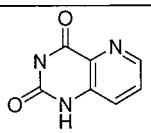
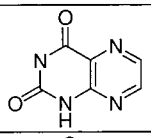
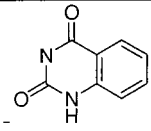
It is of interest to note that compounds with the modified pyrimidine ring (e.g., **48**) manifested the greatest level of selectivity (α_{1A} vs α_{1B}) and had very weak affinity for the α_{1D} receptor subtype. This finding distinguishes these analogues from the pyrimidinedione analogues (**40**, **43**, and **30**) and previously described tricyclic substituted benz[*e*]isoindoles like **1**. Comparison of compounds **1** and **48** could be useful tools in establishing the role of the α_{1D} receptor in treatment of BPH.

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}),[27] rat vas deferens (α_{1A}),[28] and rat spleen (α_{1B}).[28] 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 pA_2 value (Table 5). 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 (e.g., **48**) based on receptor binding affinity also exhibited the greatest selectivity in in vitro functional models.

The most α_{1A} selective compound **48** 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

Table 2. SAR of Heterocyclic Substituents

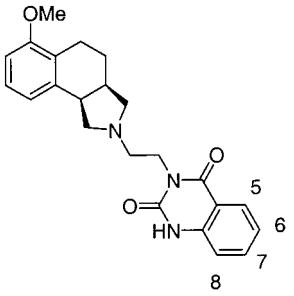


		Radioligand Binding Ki(nM)[e]			
Compound #	R	α_{1A} [a]	α_{1B} [a]	α_{1D} [a]	Selectivity ratio[d]
11*		1.39 (1.21, 1.6)	1.63 (1.43, 1.85)	0.92 (0.89, 0.91)	1.17
19		1.03 (0.93, 1.14)	2.11 (1.96, 2.28)	1.01 (0.96, 1.07)	2.04
20*		0.48 (0.42, 0.55)	1.01 (0.86, 1.20)	0.52 (0.46,0.58)	2.1
21*		1.2 [c]	2.58 [c]	1.67 [c]	2.15
22*		1.19[c]	3.31 [c]	1.99 [c]	2.78
23*		1.41 [b] (1.37, 1.46)	3.1 [b] (2.86, 3.37)	1.78 [b] (1.71, 1.86)	2.19
24*		6.80 [c]	10.57 [c]	2.87 [c]	1.55
25*		3.58 (3.00, 4.28)	8.2 (7.50, 8.98)	2.5 (2.28, 2.75)	2.29
26		9.22 [c]	12.59 [c]	5.49 [c]	1.36
27		0.67 [c]	1.16 [c]	0.62 [c]	1.73

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

measure of hypotensive liability. The IUP model used aged male anesthetized dogs, in which a pressure transducer was inserted through the urethra to the region of the prostate. Phenylephrine caused a dose-

Table 3. SAR of Mono- and Disubstituted Quinazolinediones



compound	substituent	radioligand binding K_i [f] (nM) α_{1A}[b]	α_{1B}[b]	α_{1D}[b]	selectivity ratio[e]
27		0.67[d]	1.16[d]	0.62[d]	1.73
28[a]	8-OMe	0.85 (0.75, 0.96)	2.27 (2.10, 2.45)	1.15 (1.08, 1.23)	2.67
29[a]	7-Cl[a]	0.57 (0.50, 0.64)	2.71 (1.90, 3.86)	0.58 (0.50, 0.69)	4.75
30	7-CN	0.09 (0.05, 0.15)	1.56 (1.16, 2.11)	0.77 (0.61, 0.99)	17.3
31	7-OMe	0.09 (0.05, 0.17)	0.66 (0.63, 0.68)	0.21 (0.14, 0.32)	7.3
32	7-NO_2	0.91[d]	3.33[d]	1.20[d]	3.65
33	7-$NHCOCH_3$	0.43[d]	0.84[d]	0.41[d]	1.95
34	7-COOMe	0.27[d]	1.64[c] (1.07, 2.54)	0.77[c] (0.61, 0.98)	6.07
35[a]	6-OMe	1.02 (0.88, 1.21)	3.76 (3.26, 4.33)	1.13 (1.11, 1.15)	3.68
36[a]	5-Cl	0.71 (0.57, 0.88)	0.92 (0.82, 1.04)	0.69 (0.62, 0.76)	1.31
37[a]	5-Me	1.15 (1.65, 2.17)	1.04 (0.92, 1.17)	1.13 (0.81, 1.58)	0.90
38	6-Cl,7-OMe	1.89 (1.53, 2.35)	9.27 (7.64, 11.2)	2.71 (2.15, 3.43)	4.9
39	6,7-Me	1.38[d]	4.07[d]	0.73[d]	2.94
40	6,7-OMe	0.24 (0.21, 0.28)	6.46 (6.03, 6.91)	1.40 (1.36, 1.44)	26.9
41[a]	6,8-Me	2.73[c] (2.66, 2.80)	16.28[c] (13.3, 19.9)	2.86[c] (2.72, 3.02)	5.96
42	7,8-Me	0.09 (0.05, 0.15)	1.32 ((1.15, 1.50)	0.89 (0.68, 1.17)	14.6
43	7,8-OMe	0.04 (0.03, 0.05)	0.66 (0.62, 0.71)	0.68 (0.63, 0.73)	16.5

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

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-pA_2 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 assessed in the SHR model using an ascending iv dosing paradigm and measuring the decrease in blood pressure averaged over a 60-minute 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 impact of variable pharmacokinetics between compounds. Pseudo-pA_2 values from the IUP model and pED_{50} values from the SHR model are reported in Table 6. As was found previously,[1] the absolute selectivity ratio determined in vivo is an order of magnitude greater than the in vitro selectivity ratio. The high correlation among receptor affinity, functional response in target tissues, and 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 that the α_{1B} subtype plays a prominent role in control of vascular tone.

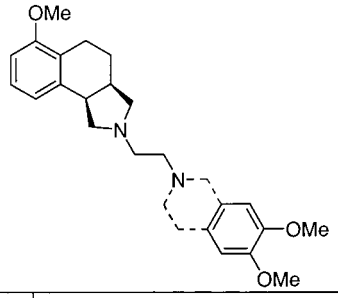
Conclusion

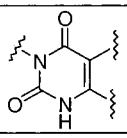
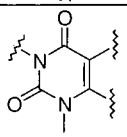
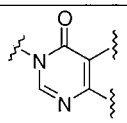
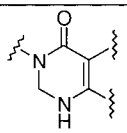
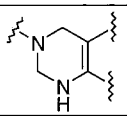
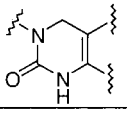
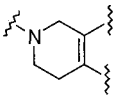
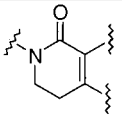
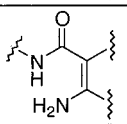
A structurally novel series of α_1 antagonists, possessing a 6-methoxybenz[*e*]isoindole unit attached to a variety of bicyclic heterocycles via a two-carbon alkyl chain, was described. It was found that selectivity was manifested only with specifically substituted quinazolinediones, where 6,7-dimethoxy compounds were the best. Further modification of the pyrimidine portion of the molecule resulted in the development of the more potent and selective pyrimidinone analogue **48**. Compound **48** showed the highest degree of selectivity in radioligand binding assays (57-fold), in vitro functional assays (80-fold), and in vivo prostate selectivity (almost 1000-fold). This correlation is further evidence that prostatic smooth muscle tone is primarily mediated by the α_{1A} subtype.

Experimental Section

1. Biology. 1.1. Radioligand Binding Assays. The compounds were evaluated for α_1 adrenoceptor binding affinity in vitro using the cloned α_{1B} (hamster) and for α_{1D} (rat) adrenoceptors expressed in LTK cells as well as for the pharmacologically defined α_{1A} adrenoceptor (rat submaxillary gland). Radioligand binding assays were performed as described previously by Knepper et al.[29] Briefly, recombinant α_1 adrenoceptors were stably expressed in mouse fibroblast cells (LTK^-) grown in roller bottle cultures to provide 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 the 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 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.[29]

Table 4. SAR of Pyrimidine Ring Modification



		Radioligand Binding Ki(nM)[e]			
Compound #	Pyrimidine modification	α_{1A} [a]	α_{1B} [a]	α_{1D} [a]	Selectivity ratio[d]
40		0.24 (0.21, 0.28)	6.46 (6.03, 6.91)	1.40 (1.36, 1.44)	26.9
46		0.25 (0.14, 0.44)	3.31 (2.87, 3.81)	3.71 (3.46, 3.98)	13.2
48		0.27 (0.23, 0.32)	15.3 (14.4, 16.2)	7.79 (6.93, 8.78)	56.6
49		12.9 [c]	95.2 [c]	71.97 [c]	7.4
52*		62.22 [c]	63.1 [c]	189 [c]	1.01
53*		122.6 [c]	191 [c]	168.2 [c]	1.5
55*		80.7 [c]	116 [c]	83.4 [c]	1.43
56*		7.82 [c]	61.2 [c]	58.4 [c]	7.83
57*		3.75 (3.68, 3.81)	29.1 (23.7, 35.6)	32.65 (29.7, 35.9)	7.8

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

1.2. 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 thiopental sodium, 15 mg/kg iv, and 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 was 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

Table 5. In Vitro Profile of Benz[*e*]isoindole Antagonists in Comparison with Other Adrenergic Antagonists

antagonist	pA_2[a] rat vas deferens	pA_2[a] rat spleen	pA_2[a] dog prostate	selectivity ratio[c]
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 ± 0.17	0.60
40	8.53 ± 0.08[b]	7.52 ± 0.03[b]	9.01 ± 0.10[b]	10.23
43	8.9 ± 0.12[b]	8.15 ± 0.01[b]	9.45 ± 0.09[b]	5.62
48	8.97 ± 0.49[b]	7.07 ± 0.16[b]	9.23 ± 0.16[b]	79.43
30	8.83 ± 0.07[b]	7.73 ± 0.04[b]	9.83 ± 0.15[b]	12.59

[a] Data expressed as a pA_2 ± SEM. Slopes are not different from unity. Number of determinations: ≥3. [b] Number of determinations: 2. [c] Selectivity ratio: antilog[pA_2(rat vas deferens)/pA_2(rat spleen)].

Table 6. Comparison of Antagonists in the IUP and SHR Models

antagonist	IUP, pseudo-pA_2 [a] (95% CL)	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
48	8.30[c] (8.09−8.51)	5.32 ± 0.32[c]	959

[a] Number of determinations: ≥3. [b] Selectivity ratio: antilog(pA_2 − pED_{50}). [c] Number of determinations: 2.

pressor effect of epinephrine were obtained before and after each dose of a test antagonist. The estimated antagonist dissociation constant (in vivo pseudo-pA_2) was determined by Schild analysis.[30]

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

2. 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 F_{254} 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.

2.1. Method A. Method A is exemplified by the following procedure for **11.**

2.1.1. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-thieno[3,2-d]-pyrimidine-2,4-(1H,3H)-dione Hydrochloride (11). 3-Amino-2-carboethoxythiophene (0.20 g, 1.15 mmol) and triphosgene (0.11 g, 0.38 mmol) were heated at reflux in toluene (25 mL) for 3 h. The reaction mixture was concentrated in vacuo to yield crude methyl 3-isocyanato-2-thiophenecarboxylate as a white crystalline compound. This isocyanate (0.21 g, 1.15 mmol) was reacted with the amine **6** (0.24 g, 1.0 mmol) in toluene (40 mL) at reflux for 3 h. The reaction mixture was then partitioned between 5% $NaHCO_3$ and hot EtOAc, and the organic phase was dried (K_2CO_3) and evaporated. The resulting product was converted to its HCl salt and recrystallized to yield **11** (0.12 g, 28%) as a white solid, mp 190−192 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.55−1.68 (m, 1H), 1.85−1.98 (m, 1H), 2.53−2.65 (m, 1H), 2.70−2.83 (m, 2H), 2.83−2.96 (m, 2H), 3.39−3.50 (m, 2H), 3.67 (q, 1H), 3.82 (s, 3H), 4.08−4.30 (m, 2H), 4.37 (t, 2H), 6.74 (t, 2H), 6.84 (d, 1H), 7.15 (t, 1H), 7.62 (d, 1H), 8.17 (bs, 1H). MS (DCI/NH_3): *m/e* 398 $(M + H)^+$. Anal. ($C_{21}H_{23}N_3O_3S\cdot HCl\cdot 0.75H_2O$) C, H, N.

2.1.2. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-methylthieno[3,2-*d*]pyrimidine-2,4(1H,3H)-dione Hydrochloride (12). The amine **6** (0.24 g, 1.0 mmol) and methyl 3-isocyanate-4-methyl-2-thiophenecarboxylate (0.22 g, 1.1 mmol) were treated by method A to yield 0.12 g of **12** as a white solid, mp 255−257 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.52 (m, 1H), 1.75 (m, 1H), 2.25 (m, 2H), 2.28 (s, 3H), 2.55 (m, 2H), 2.64−2.90 (m, 3H), 3.36−3.50 (m, 3H), 3.81 (s, 3H), 4.21 (t, 2H), 6.67 (d, 1H), 6.74 (d, 1H), 7.10 (t, 1H), 7.31 (d, 1H), 10.5 (bs, 1H). MS (DCI/NH_3): *m/e* 412 $(M + H)^+$. Anal. ($C_{22}H_{25}N_3O_3S\cdot HCl\cdot 0.5H_2O$) C, H, N.

2.1.3. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-phenylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione Methanesulfonate (13). The amine **6** (0.55 g, 2.2 mmol) and the isocyanate (0.90 g, 3.3 mmol) prepared from 2-carboethoxy-3-amino-4-phenylthiophene[23] were treated by method A to yield the free base (0.39 g, 38%) of **13**, which was converted to the methanesulfonic acid salt, mp 268−271 °C. ^{1}H NMR (DMSO-d_6): δ 1.6 (m, 1H), 1.8 (m, 1H), 2.42 (m, 2H), 2.65 (m, 2H), 3.03 (m, 3H), 3.55 (m, 3H), 3.75 (s, 3H), 4.25 (m, 2H), 6.75 (m, 1H), 6.85 (m, 1H), 7.18 (t, 1H), 7.3 (d, 1H), 7. 5 (m, 3H), 7.8 (m, 2H), 10.35 (bs, 1H). MS (DCI/NH_3): *m/e* 474 $(M + H)^+$. Anal. ($C_{28}H_{31}N_3O_6S_2\cdot 0.25H_2O$) C, H, N.

2.1.4. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-phenylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione Hydrochloride (14). The amine **6** (0.40 g, 1.6 mmol) and the isocyanate (0.54 g, 2.1 mmol) derived from 2-carboethoxy-3-amino-5-phenylthiophene[22] were treated by method A to yield **14** (0.39 g, 38%) as a white solid, mp 229−231 °C. ^{1}H NMR (DMSO-d_6): δ 1.6 (m, 1H), 1.8 (m, 1H), 2.45 (m, 2H), 2.72 (m, 2H), 3.05 (m, 3H), 3.55 (m, 3H), 3.75 (s, 3H), 4.25 (m, 2H), 6.8 (m, 2H), 7.18 (t, 1H), 7.5 (m, 5H), 8.1 (m, 1H), 10.35 (s, 1H). MS (DCI/NH_3): *m/e* 474 $(M + H)^+$. Anal. ($C_{27}H_{27}N_3O_3S\cdot HCl\cdot 0.5H_2O$) C, H, N.

2.1.5. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-6-methoxythieno-[3,2-d]pyrimidine-2,4(1H,3H)-dione Fumarate (15). A 2.5 M *n*-BuLi (4.0 mL, 10 mmol) sample was added to MeOH (404 mL, 10 mmol) in THF (10 mL) at 0 °C under nitrogen. After the mixture was stirred for 20 min, CS_2 (600 mL, 10 mmol) was added and stirring was continued for 4 h. The reaction was then cooled to 0 °C followed by the addition of MeI (620 mL, 10 mmol), whereupon the reaction mixture was stirred for 4 h at 0 °C and then at ambient temperature overnight. In a separate flask the anion of acetonitrile was prepared by the dropwise addition of MeCN (520 mL, 10 mmol) to a solution of LDA (10 mmol) in THF at −78 °C followed by stirring for 30 min at that temperature. The solution of the xanthate prepared above was added to the acetonitrile anion. The reaction mixture was stirred for 1 h at −78 °C, then 1 h at 0 °C. The reaction mixture was then cooled to −78 °C, treated with ethyl bromoacetate (1.1 mL, 10 mmol), warmed to room temperature, treated with 1.0 M lithium bistrimethylsilylamide (1 mL), and heated at reflux for 1.5 h. After cooling, the reaction mixture was partitioned between saturated $NaHCO_3$ solution and CH_2Cl_2. The organic layer was dried with sodium

sulfate, filtered, concentrated in vacuo, and chromatographed on silica gel eluting with 4:1 hexanes/EtOAc to give 0.343 g (17%) of 5-amino-4-carboethoxy-2-methoxythiophene. 5-Amino-4-carboethoxy-2-methoxythiophene (0.3 g, 1.51 mmol) in CH_2Cl_2 was cooled to −78 °C and treated with 1.93 M solution of phosgene in toluene (0.082 mL, 1.55 mmol) in the presence of triethylamine (0.045 mL). After 1 h at −78 °C the solution of the amine **6a** (0.375 g, 1.52 mmol) in CH_2Cl_2 was added to the reaction mixture. After being stirred for 1 h, the reaction mixture was quenched into $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to yield the corresponding urea. This was dissolved in THF, and 1.7 mL of 1.0 M potassium *tert*-butoxide was added to the solution. After 1 h at 60 °C the reaction mixture was neutralized with 1 N HCl and extracted with EtOAc (3×). The combined organic layers were dried (Na_2SO_4) and evaporated to give the crude product that was chromatographed on silica gel eluting with 3% Et_3N/3% MeOH/EtOAc to yield **15** (0.24 g, 38%) as a free base that was converted to the fumarate salt, mp 217 °C. ^{1}H NMR (DMSO-d_6): δ 1.45 (1H, m), 1.65 (1H, m), 2.23 (1H, m), 2.32 (1H, m), 2.44 (2H, m), 2.58 (1H, m), 2.66 (2H, m), 3.30 (3H, m), 3.75 (3H, s), 3.95 (2H, t), 3.99 (3H, s), 6.10 (1H, s), 6.59 (2H, s), 6.72 (1H, d), 6.75 (1H, d), 7.09 (1H, t), 11.76 (1H, br s). Anal. ($C_{26}H_{29}N_3O_8S$) C, H, N.

2.1..6. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-6-carbomethoxythieno[3,2-d]pyrimidine-2,4(1H,3H)-dione Hydrochloride (16). To a slurry of compound **11** (0.39 g, 1 mmol) in THF cooled to −5 °C was slowly added 2.1 equiv of LDA solution. After the mixture was stirred at this temperature for 1 h, methylformate (0.08 mL, 1 mmol) was added. The reaction mixture was stirred for another hour at 0 °C, then it was quenched into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel, eluting with 18:1:1 EtOAc/H_2O/HCOOH to yield **16** (0.11 g, 24%) as its formic acid salt. It was converted to HCl salt and triturated with EtOH/toluene to form an amorphous solid. ^{1}H NMR ($CDCl_3$) (free base): δ 1.55 (m, 1H), 1.8 (m, 1H), 2.38 (m, 2H), 2.5−2.75 (m, 3H), 3.02 (m, 1H), 3.12 (m, 1H), 3.48 (m, 1H), 3.73 (m, 2H), 3.8 (s, 3H), 3.95 (s, 3H), 4.25 (m, 2H), 6.65 d, 1H), 6.76 (d, 1H), 7.09 (t, 1H), 7.15 (s, 1H). MS (DCI/NH_3): *m/e* 456 (M + H)$^+$. Anal. ($C_{23}H_{25}N_3O_5S$·HCl) C, H, N.

2.1..7. 3-[2-((3aR,9bR)-*cis*-6-Methoxy2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-6-methoxy-7-methylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione Hydrochloride (17). 4-Amino-5-carboethoxy-2-methoxy-3-methylthiophene (0.46 g, 1.93 mmol) prepared by the method described for **15**, substituting propionitrile for MeCN, and the amine **6a** (0.49 g, 2 mmol) were reacted as described in the procedure for **15** to yield the free base of **17** (0.42 g), which was converted to HCl salt, mp 205 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.45 (1H, m), 1.65 (1H, m), 2.0(s, 3H), 2.1−2.32 (2H, m), 2.44 (2H, m), 2.6 (2H, m), 3.30 (3H, m), 3.75 (3H, s), 3.95 (2H, m), 3.99 (3H, s), 6.72 (1H, d), 6.75 (2H, m), 7.09 (1H, t). MS (DCI/NH_3): *m/e* 442 (M + H).$^+$ Anal. ($C_{23}H_{27}N_3O_4S$ ·HCl·0.25H_2O) C, H, N.

2.1..8. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-isopropyl-6-methoxythieno[3,2-d]pyrimidine-2,4(1H,3H)-dione Hydrochloride (18). 4-Amino-3-isopropyl-5-carboethoxy-2-methoxythiophene (0.33 g, 1.36 mmol), prepared by the method described for **15**, substituting isovaleronitrile for acetonitrile, and the amine **6a** were reacted as described in the procedure for **15** to yield the free base of **18** (0.22 g, 34%), which was converted to HCl salt. ^{1}H NMR ($CDCl_3$) (free base): δ 1.29 (s,-3H), 1.31 (s, 3H), 1.55 (m, 1H), 1.75 (m, 1H), 2.28 (m, 2H), 2.55 (m, 2H), 2.62−2.85 (m, 3H), 3.05 (m, 1H), 3.41 (m, 3H), 3.8 (s, H), 4.0 (s, 3H), 4.18 (t, 2H), 6.68 (d, 1H), 6.72 (d, 1H), 6.95 (t, 1H). MS (DCI/NH_3): *m/e* 470(M + H)$^+$. Anal. ($C_{25}H_{31}N_3O_4S$·HCl) C, H, N.

2.2. Method B. Method B is exemplified by the following procedure for **19**.

2.2.1. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione Hydrochloride (19). 2-Amino-3-carboethoxythiophene, prepared by the method of Gewald,[31] was treated with 2-chloroethylisocyanate.[20] The resulting urea (1.65 g, 6.0 mmol), the benz[*e*]isoindole **5a** (1.10 g, 5.4 mmol), and diisopropylethylamine (1 mL) in DMSO (2 mL) were heated at 100 °C for 2 h. The reaction mixture was quenched in water and extracted with EtOAc. The combined organic extracts were dried and concentrated in vacuo, resulting in the urea ester intermediate, which was treated with 1.0 M KOtBu (0.6 mL) in EtOH (6 mL) at reflux for 0.5 h. The reaction mixture was evaporated, and the residue was chromatographed on silica gel, eluting with EtOAc/EtOH (95:5) to yield **19** (0.91 g (39%) as a free base that was converted to the HCl salt, mp 179−182 °C (dec). ^{1}H NMR (free base) ($CDCl_3$): δ 1.52−1.66 (m, 1H), 1.80−1.92 (m, 1H), 2.49−2.65 (m, 3H), 2.69−2.83 (m, 2H), 3.18−3.38 (m, 2H), 3.59−3.70 (m, 1H), 3.82 (s, 3H), 3.96−4.10 (m, 2H), 4.30 (bt, 2H), 6.49 (d, 1H), 6.70 (d, 1H), 6.79 (d, 1H), 6.93 (d, 1H), 7.13 (t, 1H). MS (DCI/NH_3): *m/e* 398 (M + H)$^+$. Anal. ($C_{21}H_{23}N_3O_3S$·HCl·1.5H_2O) C, H, N.

2.2.2. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-thieno[3,4-d]pyrimidine-2,4-(1H,3H)-dione Hydrochloride (20). The amine **6** (0.30 g, 1.2 mmol) and the isocyanate derived from 3-amino-4-carboethoxythiophene[32] were treated by method A to yield **20** (0.15 g, 45%) as a white solid, mp 205−210 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.54−1.88 (m, 1H), 1.82−1.94 (m, 1H), 2.52−2.65 (m, 1H), 2.71−2.86 (m, 4H), 3.25−3.38 (m, 2H), 3.66−3.79 (m, 1H), 3.83 (s, 3H), 3.98−4.18 (m, 2H), 4.29 (t, 2H), 6.55 (d, 1H), 6.71 (d, 1H), 6.77 (d, 1H), 7.13 (t, 1H), 8.10 (d, 1H), 10.2 (bs, 1H). MS (DCI/NH_3): *m/e* 398 (M + H)$^+$. Anal. ($C_{21}H_{23}N_3O_3S$·HCl·1.5H_2O) C, H, N.

2.2.3. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione Fumarate (21). 2-Amino-3,4-bis(ethoxycarbonyl)pyrrole[33] was reacted with 2-chloroethylisocyanate by method B. The intermediate urea (0.60 g, 2.1 mmol) was reacted with the benz[*e*]isoindole **5** (0.41, 2 mmol) as in **19.** The urea ester intermediate was treated with 5% KOH (50 mL) and heated at 110 °C for 1 h. After the mixture was cooled to room temperature, the pH of the reaction mixture was adjusted to 12 by the addition of concentrated HCl, resulting in the precipitation of the product. The product was extracted with CH_2Cl_2, and the organic layer was dried and evaporated to give 0.19 g of **21** as a free base that was converted to the fumaric acid salt. ^{1}H NMR (CD_3OD): δ 1.62 (m, 1H), 1.90 (m, 1H), 2.58 (m, 1H), 2.78 (m, 1H), 2.82 (dt, 1H), 3.18 (m, 2H), 3.40 (t, 2H), 3.62 (dd, 1H), 3.81 (s, 3H), 3.86 (dd, 1H), 4.01 (dd, 1H), 4.33 (t, 2H), 6.42 (d, 1H), 6.64 (d, 1H), 6.65 (s, 2H), 6.77 (d, 1H), 6.81 (d, 1H), 7.15 (t, 1H). MS (DCI/NH_3): *m/e* 381 (M + H)$^+$. Anal. ($C_{25}H_{28}N_4O_7$·0.75H_2O) C, H, N.

2.2.4. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-pyrido[2,3-d]pyrimidine-2,4-(1H,3H)-dione Hydrochloride (22). 2-Amino-3-ethoxycarbonylpyridine (0.46 g, 2.8 mmol), prepared from 2-aminonicotinic acid by the procedure described for 3-aminopicolinic acid,[24] was converted to the isocyanate in situ as described for **15** and reacted with the amine **6** (2.8 mmol) by method A to yield **22**, mp 234−236 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.47−1.61 (m, 1H), 1.72−1.86 (m, 1H), 2.27 (q, 2H), 2.49−2.61 (m, 1H), 2.64−2.77 (m, 2H), 2.84−2.95 (m, 1H), 3.05−3.16 (m, 1H), 3.53 (q, 1H), 3.76 (t, 2H), 3.80 (s, 3H), 4.17−4.35 (m, 2H), 6.67 (d, 1H), 6.77 (d, 1H), 6.90−6.96 (m, 1H), 7.09 (t, 1H), 8.05 (dt, 1H), 8.48 (dd, 1H). MS (DCI/NH_3): *m/e* 393 (M + H)$^+$. Anal. ($C_{22}H_{24}N_4O_3$·HCl·0.75H_2O) C, H, N.

2.2.5. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-pyrido[3,4-d]pyrimidine-2,4-(1H,3H)-dione Dihydrochloride (23). 3-Amino-4-ethoxycarbonylpyridine (0.58 g, 3,5 mmol), prepared from 3,4-pyridinedicarboxyimide by the literature procedure,[24] and the benz[*e*]isoindole **5a** (0.60 g, 2.4 mmol) were reacted as described for **15** to yield 0.68 g (71%) of **23**, which was converted to its HCl salt, mp 228−230 °C. ^{1}H NMR (CD_3OD) (free base):

δ 1.45−1.49 (m, 1H), 1.66−1.78 (m, 1H), 2.22 (t, 1H), 2.33 (dt, 1H), 2.50−2.68 (m, 3H), 2.77−2.86 (m, 2H), 3.24−3.51 (m, 3H), 3.77 (s, 3H), 4.20 (t, 2H), 6.71 (dd, 2H), 7.07 (t, 1H), 7.91 (d, 1H), 8.39 (d, 1H), 8.55 (s, 1H). MS (DCI/NH_3): *m/e* 393 $(M + H)^+$. Anal. ($C_{22}H_{24}N_4O_3$·2 HCl) C, H, N.

2.2.6. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-pyrido[4,3-d]pyrimidine-2,4-(1H,3H)-dione Dihydrochloride (24). 4-Amino-3-ethoxycarbonylpyridine[25] (0.57 g, 3.4 mmol) and the amine **6** (0.60 g, 2.4 mmol) were reacted as described for **15** to yield 0.69 g (72%) of **24**, which was converted to its HCl salt, mp 229−233 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.49−1.62 (m, 1H), 1.75−1.87 (m, 1H), 2.38 (t, 2H), 2.50−2.77 (m, 3H), 2.88−2.98 (m, 1H), 3.09−3.20 (m, 1H), 3.47 (q, 1H), 3.69 (bt, 2H), 3.80 (s, 3H), 4.15−4.37 (m, 2H), 6.63 (d, 1H), 6.67 (d, 1H), 6.78 (d, 1H), 7.10 (t, 1H), 8.47 (d, 1H), 8.98 (s, 1H). MS (DCI/NH_3): *m/e* 393 $(M + H)^+$. Anal. ($C_{22}H_{24}N_4O_3$·2 HCl·1.5H_2O) C, H, N.

2.2.7. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-pyrido[3,2-d]pyrimidine-2,4-(1H,3H)-dione Hydrochloride (25). 3-Amino-2-ethoxycarbonylpyridine[24] (0.30 g, 1.8 mmol) and the amine **6** (0.40 g, 1.6 mmol) were reacted as described for **15** to yield 0.51 g (80%) of **25**, which was converted to its HCl salt, mp 195−198 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.47−1.62 (m, 1H), 1.74−1.87 (m, 1H), 2.47 (t, 2H), 2.50−2.76 (m, 3H), 2.97−3.07 (m, 1H), 3.13−3.25 (m, 1H), 3.46 (q, 1H), 3.70−3.83 (m, 2H), 3.78 (s, 3H), 4.24−4.43 (m, 2H), 6.65 (d, 1H), 6.77 (d, 1H), 7.07 (d, 1H), 7.12 (d, 1H), 7.31 (dd, 1H), 8.25 (d, 1H). MS (DCI/NH_3): *m/e* 393 $(M + H)^+$. Anal. ($C_{22}H_{24}N_4O_3$·HCl·1.25H_2O) C, H, N.

2.2.8. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-2,4-pteridinedione Hydrochloride (26). Methyl 3-amino-2-pyrazinecarboxylate (10 g, 65.2 mmol) was treated with 2-chloroethylisocyanate[20] (5.6 mL, 65.2 mmol) to yield 1.1 g of chloroethyl urea. The urea (0.264 g, 1.02 mmol) and **5a** (0.2, 1.0 mmol) were reacted by method B as in **19** and chromatographed on silica gel, eluting with EtOAc/HCOOH/H_2O (8:1:1) to yield the formic acid salt of **26** that was converted to HCl salt, mp 310−312 °C.

^{1}H NMR (DMSO-d_6): δ 1.47 (m, 1H), 1.62 (m, 1H), 2.11−2.28 (m, 2H), 2.4−2.68 (m, 1H), 3.18−3.31 (m, 3H), 3.78 (s, 3H), 4.0 (t, 2H), 6.78 (m, 1H), 6.82 (d, 2H), 7.09 (t, 1H), 7.85 (m, 1H), 8.36 (d, 1H), 8.65 (d, 1H). Anal. ($C_{21}H_{23}N_5O_3$·HCl·1.25H_2O) C, H, N.

2.2.9. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]quinazoline-2,4(1H,3H)-dione Hydrochloride (27). 2-Carboethoxyphenylisocyanate (0.20 g, 1.0 mmol) and the amine **6** (0.24 g, 1.0 mmol) were reacted by method A to yield 0.12 g of **27** as a white solid. ^{1}H NMR (DMSO-d_6): δ 1.37−1.5 (m, 1H), 1.57−1.68 (m, 1H), 2.1−2.3 (m, 2H), 2.38−2.48 (m, 2H), 2.52−2.65 (m, 3H), 3.12−3.3 (m, 3H), 3.73 (s, 3H), 4.02 (t, 2H), 6.72 (dd, 2H), 7.08 (t, 1H), 7.12−7.27 (m, 2H), 7.65 (t, 1H), 7.92 (d, 1H). Anal. ($C_{23}H_{25}N_3O_3$·HCl·H_2O) C, H, N.

2.2.10. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-8-methoxyquinazoline-2,4-(1H,3H)-dione Hydrochloride (28). The amine **6** (0.25 g, 1.0 mmol) and the isocyanate (0.30 g, 1.1 mmol) prepared from 2-methoxy-6-carboethoxyaniline were reacted by method A to yield **28** (0.15 g, 33%) as a white solid, mp 233−235 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.52−1.68 (m, 1H), 1.88−1.98 (m, 1H), 2.51−2.63 (m, 1H), 2.7−2.98 (m, 4H), 3.41 (m, 2H), 3.68 (q, 1H), 3.82 (s, 3H), 3.98 (s, 3H), 4.1−4.28 (m, 2H), 4.42 (m, 2H), 6.75 (t, 2H), 7.08−7.2 (m, 3H), 7.68 (dd, 1H). MS (DCI/NH_3): *m/e* 422 $(M + H)^+$. Anal. ($C_{24}H_{27}N_3O_4$·HCl·1.25H_2O) C, H, N.

2.2.11. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-chloroquinazoline-2,4(1H,-3H)-dione Hydrochloride (29). The amine **6** (0.25 g, 1.0 mmol) and the isocyanate (0.26 g, 1.25 mmol) prepared from 2-carboethoxy-5-chloroaniline were reacted by method A to yield **29** (0.12 g, 25%) as a white solid, mp >250 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.52−1.68 (m, 1H), 1.7−1.86 (m, 1H), 2.6−2.85 (m, 2H), 2.92−3.1 (m, 2H), 3.42−3.58 (m, 4H), 3.78 (s, 3H), 3.95−4.3 (m, 4H), 6.75 (m, 1H), 6.84 (m, 1H), 7.18 (t, 1H), 7.28 (m, 2H), 7.95 (m, 1H). MS (DCI/NH_3): *m/e* 426 $(M + H)^+$. Anal. ($C_{23}H_{24}N_3O_3Cl$·HCl·0.25H_2O) C, H, N.

2.2.12. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-cyanoquinazoline-2,4(1H,3H)-dione Hydrochloride (30). The amine **6a** (0.41 g, 1.7 mmol) and the isocyanate (0.36 g, 1.8 mmol), prepared from the 2-carboethoxy-5-cyanoaniline,[34] were reacted by method A and chromatographed on silica gel (18:1:1 EtOAc/H_2O/HCOOH) to yield the formic acid salt of **30** that was converted to HCl salt (0.24 g, 35%), mp >250 °C. ^{1}H NMR (DMSO-d_6): δ 1.54−1.68 (m, 1H), 1.70−1.85 (m, 1H), 2.43−2.53 (m, 1H), 2.55−2.82 (m, 2H), 2.93−3.10 (m, 1H), 3.40−3.55 (m, 4H), 3.77 (s, 3H), 3.97−4.30 (m, 4H), 6.73−6.90 (m, 2H), 7.17 (t, J = 8 Hz, 1H), 7.58−7.65 (m, 2H), 8.10 (d, J = 8 Hz, 1H), 10.40 (bs, 1H), 11.92 (s, 1H). MS (DCI/NH_3): *m/e* 417 $(M + H)^+$. Anal. ($C_{24}H_{24}N_4O_3$·HCl·0.35H_2O) C, H, N.

2.2.13. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-methoxyquinazoline-2,4(1H,3H)-dione Hydrochloride (31). The amine **6a** (0.42 g, 1.7 mmol) and the isocyanate (0.37 g, 1.8 mmol), prepared from 2-carboethoxy-5-methoxyaniline,[35] were reacted by method A to yield **31** (0.32 g, 45%) as a tan solid, mp 226−230 °C. ^{1}H NMR (DMSO-d_6): δ 1.70−1.85 (m, 1H), 1.54−1.68 (m, 1H), 2.43−2.53 (m, 1H), 2.55−2.82 (m, 2H), 2.93−3.10 (m, 1H), 3.40−3.55 (m, 4H), 3.77 (s, 3H), 3.85 (s, 3H), 3.97−4.30 (m, 4H), 6.73−6.90 (m, 4H), 7.17 (t, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 10.25 (bs, 1H), 11.50 (s, 1H). MS (DCI/NH_3): *m/e* 422 $(M + H)^+$. Anal. ($C_{24}H_{27}N_3O_4$·HCl·0.3H_2O) C, H, N.

2.2.14. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-nitroquinazoline-2,4(1H,3H)-dione Hydrochloride (32). 2-Carboethoxy-5-nitroaniline (4.74 g, 22.6 mmol), prepared from 2-amino-4-nitrobenzoic acid, and 2-chloroethylisocyanate (2.5 mL, 29.4 mmol) in toluene (50 mL) were heated at reflux for 16 h. Solvent was evaporated, and the remaining residue was triturated with ethyl acetate to provide a crystalline urea (1.3 g). The benz[*e*]isoindole **5** (0.66 g, 3.25 mmol) and the intermediate urea (1.23 g, 3.9 mmol) were reacted by method B to yield, after chromatography on silica gel (18:1:1 EtOAc/H_2O/HCOOH), **32** (0.4 g, 29%) as its formic acid salt, which was converted to the HCl salt. ^{1}H NMR ($CDCl_3$) (free base): δ 1.52−1.68 (m, 1H), 1.7−1.86 (m, 1H), 2.45 (m, 2H), 2.52−2.78 (m, 3H), 3.05 (m, 2H), 3.5 (m, 1H), 3.68 (m, 2H), 3.78 (s, 3H), 4.3 (m, 2H), 6.68 (d, 1H), 6.78 (d, 1H), 7.09 (t, 1H), 7.7 (s, 1H), 7.78 (d, 1H), 7.95 (d, 1H). MS (DCI/NH_3): *m/e* 437 $(M + H)^+$. Anal. ($C_{23}H_{24}N_4O_5$·HCl·0.5H_2O) C, H, N.

2.2.15. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-acetamidoquinazoline-2,4(1H,3H)-dione Hydrochloride (33). Compound **32** (0.3 g, 0.68 mmol) in MeOH was hydrogenated at 4 atm over 10% Pd/C catalyst to yield 0.18 g of an intermediate aniline. The aniline (0.15 g, 0.37 mmol) was stirred at room temperature for 24 h in CH_2Cl_2 with pyridine (0.045 mL) and acetic anhydride (0.049 mL). Solvents were removed in vacuo, and the residue was chromatographed on silica gel (18:1:1 EtOAc/H_2O/HCOOH) to yield **33** (0.66 g, 66%), which was converted to the HCl salt, mp 255−257 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.6 (m, 1H), 1.8 (m, 1H), 2.1 (s, 3H), 2.3−2.5 (m, 5H), 3.05 (m, 2H), 3.5 (m, 3H), 3.78 (s, 3H), 4.2 (m, 2H), 6.75 (m, 1H), 6.85 (m, 1H), 7.18 (t, 1H), 7.3 (d, 1H), 7.78 (d, 1H), 7.88 (t, 1H). MS (DCI/NH_3): *m/e* 449 $(M + H)^+$. Anal. ($C_{25}H_{28}N_4O_4$·HCl·H_2O) C, H, N

2.2.16. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7-carbomethoxy-2,4(1H,3H)-dione Hydrochloride (34). The amine **6a** (1.35 g, 5.5 mmol) and the isocyanate (1.41 g, 6 mmol) prepared from dimethylaminoterephthalate were reacted by method A to yield **34** (1.4, 57%) as a white solid, mp 228−230 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.52−1.68 (m, 1H), 1.7−1.86 (m, 1H), 2.32 (m, 2H), 2.52−2.75 (m, 3H), 2.92−3.1 (m, 2H), 3.5 (m, 1H), 3.66 (m, 2H), 3.8 (s, 3H), 3.98 (s, 3H), 4.28 (t, 2H), 6.66 (d, 1H), 6.78 (d, 1H), 7.1 (t, 1H), 7.5 (s, 1H),

7.6 (d, 1H), 7.82 (d, 1H). MS (DCI/NH_3): *m/e* 450 $(M + H)^+$. Anal. ($C_{25}H_{27}N_3O_5 \cdot HCl \cdot 0.25H_2O$) C, H, N.

2.2.17. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-6-methoxyquinazoline-2,4-(1H,3H)-dione Hydrochloride (35). The amine **6** (0.32 g, 1.3 mmol) and the isocyanate (0.33 g, 1.5 mmol), prepared from 2-carboethoxy-4-methoxyaniline, were reacted by method A to yield **35** (0.129 g, 25%) as a white solid, mp 159−161 °C. ^{1}H NMR (DMSO-d_6): δ 1.55−1.68 (m, 1H), 1.7−1.9 (m, 1H), 2.6−2.85 (m, 2H), 2.95−3.1 (m, 2H), 3.4−3.6 (m, 4H), 3.6−3.8 (m, 1H), 3.78 (s, 3H), 3.8 (s, 3H), 3.98−4.18 (m, 3H), 6.7−6.88 (m, 2H), 7.18 (m, 2H), 7.35 (m, 2H). MS (DCI/NH_3): *m/e* 422 $(M + H)^+$. Anal. ($C_{24}H_{27}N_3O_4 \cdot HCl \cdot H_2O$) C, H, N.

2.2.18. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-5-chloroquinazoline-2,4(1H,-3H)-dione Hydrochloride (36). The amine **6** (0.40 g, 1.6 mmol) and the isocyanate (0.44 g, 2.1 mmol) prepared from 2-carboethoxy-3-chloroaniline were reacted by method A to yield **36** (0.12 g, 18%) as a white solid, mp >250 °C (dec). ^{1}H NMR ($CDCl_3$) (free base): δ 1.55−1.7 (m, 1H), 1.87−1.98 (m, 1H), 2.52−2.65 (m, 1H), 2.7−2.84 (m, 2H), 2.87−3.0 (m, 2H), 3.4−3.57 (m, 2H), 3.68 (q, 1H), 3.82 (s, 3H), 4.1−4.42 (m, 4H), 6.73 (dd, 2H), 7.0 (d, 2H), 7.18 (m, 2H), 7.35 (m, 2H). MS (DCI/NH_3): *m/e* 426 $(M + H)^+$. Anal. ($C_{23}H_{24}N_3O_3Cl \cdot HCl \cdot 2H_2O$) C, H, N.

2.2.19. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-5-methylquinazoline-2,4(1H,-3H)-dione Hydrochloride (37). The amine **6** (0.28 g, 1.1 mmol) and the isocyanate (0.28 g, 1.4 mmol) prepared from 2-carbomethoxy-3-methylaniline were reacted by method A to yield **37** (0.16 g, 28%) as a white solid, mp 178−180 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.53−1.7 (m, 1H), 1.87−2.0 (m, 1H), 2.51−2.65 (m, 1H), 2.73 (s, 3H), 2.7−2.85 (m, 2H), 2.93−3.06 (m, 2H), 3.4−3.58 (m, 2H), 3.68 (q, 1H), 3.82 (s,3H), 4.1 (m, 2H), 4.2 (t, 2H), 6.72 (dd, 2H), 6.92 (dd, 2H), 7.17 (t, 1H), 7.38 (t, 1H). MS (DCI/NH_3): *m/e* 406 $(M + H)^+$. Anal. ($C_{24}H_{27}N_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

2.2.20. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-6-chloro-7-methoxyquinazoline-2,4(1H,3H)-dione Hydrochloride (38). The amine **6a** (0.42 g, 1.7 mmol) and the isocyanate (0.43 g, 1.8 mmol) prepared from 2-carbomethoxy-4-chloro-3-methoxyaniline [35] were reacted by method A to yield **38** (0.44 g, 57%) as a white solid, mp 218−220 °C. ^{1}H NMR (DMSO-d_6): δ 1.54−1.68 (m, 1H), 1.70−1.85 (m, 1H), 2.43−2.53 (m, 1H), 2.55−2.82 (m, 2H), 2.93−3.10 (m, 1H), 3.40−3.55 (m, 4H), 3.77 (s, 3H), 3.94 (s, 3H), 3.97−4.30 (m, 4H), 6.73−6.90 (m, 3H), 7.17 (t, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 10.40 (bs, 1H), 11.75 (s, 1H). MS (DCI/NH_3): *m/e* 456 $(M + H)^+$. Anal. ($C_{24}H_{26}N_3O_4Cl \cdot HCl \cdot 0.3H_2O$) C, H, N.

2.2.21. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-6,7-dimethylquinazoline-2,4(1H,3H)-dione Hydrochloride (39). The amine **6a** (0.5 g, 2 mmol) and the isocyanate (0.7 g, 2.1 mmol) prepared from 2-carboethoxy-4,5-dimethylaniline[21] were reacted by method A to yield **39** (0. 3 g, 54%), mp 185−188 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.52−1.68 (m, 1H), 1.73−1.88 (m, 1H), 2.22 (s, 3H), 2.28 (s, 3H), 2.28−2.38 (m, 2H), 2.5−2.75 (m, 2H), 2.7−3.15 (m, 2H), 3.42 (m, 2H), 3.63 (m, 2H), 3.83 (s, 3H), 4.25 (t, 2H), 6.65 (d, 1H), 6.68 (s, 1H), 6.76 (d, 1H), 7.11 (t, 1H), 7.66 (s, 1H). MS (DCI/NH_3): *m/e* 420 $(M + H)^+$. Anal. ($C_{25}H_{29}N_3O_3 \cdot HCl \cdot 0.75H_2O$) C, H, N.

2.2.22. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione Hydrochloride (40). The amine **6a** (0.6 g, 2.44 mmol) and the isocyanate (0.7 g, 2.46 mmol) derived from 2-carboethoxy-4,5-dimethoxyaniline were treated by method A to yield **40** (0.6 g, 54%). ^{1}H NMR (DMSO-d_6): δ 1.52−1.68 (m, 1H), 1.73−1.88 (m, 1H), 2.6−2.85 (m, 2H), 2.92−3.6 (m, 2H), 3.42 (m, 3H), 3.65 (m, 1H), 3.8 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 3.9−4.1 (m, 1H), 4.2−4.32 (m, 3H), 6.75 (d, 1H), 6.81 (s, 1H), 6.85 (d, 1H), 7.18 (t, 1H), 7.36 (s, 1H). Anal. ($C_{25}H_{29}N_3O_5 \cdot HCl \cdot H_2O$) C, H, N.

2.2.23. 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-6,8-dimethylquinazoline-2,4-(1H,3H)-dione Hydrochloride (41). The amine **6** (0.46 g, 1.6 mmol) and the isocyanate (0.45 g, 2.1 mmol) prepared from 2-carboethoxy-4,6-dimethylaniline[21] were treated by method A to yield **41** (0.22 g, 30%) as a white solid, mp 273−4 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.48−1.68 (m, 1H), 1.72−1.85 (m, 1H), 2.3 (s, 3H), 2.33 (s, 3H), 2.6−2.83 (m, 2H), 2.88−3.1 (m, 2H), 3.4−3.58 (m, 4H), 3.8 (s, 1H), 3.8−4.1 (m, 1H), 4.08−4.2 (m, 1H), 4.2−4.3 (m, 2H), 6.7−6.9 (m, 2H), 7.18 (t, 1H), 7.39 (s, 1H), 7.62 (s, 1H). MS (DCI/NH_3): *m/e* 420 $(M + H)^+$. Anal. ($C_{25}H_{29}N_3O_3 \cdot HCl$) C,H,N.

2.2.24. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7,8-dimethylquinazoline-2,4(1H,3H)-dione Hydrochloride (42). The amine **6a** (0.5 g, 2 mmol) and the isocyanate (0.53 g, 2.1 mmol) prepared from 2,3-dimethyl-6-carboethoxyaniline[21] were treated by method A to yield **42** (0. 6 g, 70%), which was converted to the HCl salt, mp 210−12 °C (EtOH/EtOAc). ^{1}H NMR ($CDCl_3$) (free base): δ 1.45−1.59 (m, 1H), 1.69−1.8 (m, 1H), 2.28 (s, 3H), 2.39 (s, 3H), 2.48−2.6 (m, 2H), 2.6−2.88 (m, 3H), 2.7−3.15 (m, 2H), 3.42 (m, 3H), 3.83 (s, 3H), 4.22 (t, 2H), 6.68 (d, 1H), 6.75 (d, 1H), 7.05 (d, 1H), 7.11 (t, 1H), 7.69 (s, 1H), 8.5 (s, 1H). MS (DCI/NH_3): *m/e* 420 $(M + H)^+$. Anal. ($C_{25}H_{29}N_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

2.2.25. 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-7,8-dimethoxyquinazoline-2,4(1H,3H)-dione Hydrochloride (43). The amine **6a** (0.5 g, 2 mmol) and the isocyanate (0.56 g, 2.1 mmol) prepared from 2,3-dimethoxy-6-carboethoxyaniline[39] were treated by method A to yield **43** (0. 5 g, 55%), which was converted to HCl salt, mp 174−176 °C (EtOH/Et_2O). ^{1}H NMR ($CDCl_3$) (free base): δ 1.45−1.59 (m, 1H), 1.69−1.8 (m, 1H), 2.21−2.32 (m, 2H), 2.48−2.62 (m, 2H), 2.62−2.85 (m, 3H), 2.62−2.85 (m, 3H), 3.81 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 4.2 (t, 2H), 6.68 (d, 1H), 6.75 (d, 1H), 6.7 (d, 1H), 7.1 (t, 1H), 7.82 (d, 1H), 8.22 (s, 1H). MS (DCI/NH_3): *m/e* 452 $(M + H)^+$. Anal. ($C_{25}H_{29}N_3O_3 \cdot HCl \cdot H_2O$) C, H, N.

2.2.26. Methyl 4,5-Dimethoxy-2-(methylamino)-benzoate (44). A sample of 96% HCOOH (1.22 mL) was added to the cooled to 0 °C acetic anhydride (2.7 g, 26 mmol), and the reaction mixture was heated at 50 °C for 2 h, cooled to room temperature, and diluted with THF.[26] A solution of methyl 2-amino-4,5-dimethoxybenzoate (2.1 g, 10 mmol) in THF (30 mL) was added to that reagent, and the reaction mixture was stirred at room temperature for 1 h and then concentrated to $^1/_2$ of the volume. The resulting methyl 2-(formylamino)-4,5-dimethoxybenzoate (0.95 g) was filtered off as a white solid. ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H), 3.91 (s, 3H), 3.98 (s, 3H), 7.48 (s, 1H), 8.42 (s, 1H), 8.49 (d, 1H), 11.06 (s, 1H).

A solution of 10 M $BH_3 \cdot (CH_3)_2S$ (1 mL) was added to a suspension of methyl 2-(formylamino)-4,5-dimethoxybenzoate (0.95 g, 4 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 2 h, diluted with THF (30 mL), and treated with TMEDA (4 mL). After the mixture was stirred at room temperature for 2 h, the reaction mixture was partitioned between dilute $NaHCO_3$ and EtOAc. The organic layer was washed with H_2O and then with brine, dried ($MgSO_4$), and evaporated. The obtained residue was chromatographed on silica gel, eluting with 30% EtOAc/hexane to yield 0.5 g of **44** as a white crystalline substance. ^{1}H NMR ($CDCl_3$): δ 2.93 (d, 3H), 3.82 (s, 6H), 3.92 (s, 3H), 6.1 (s, 1H), 7. 38 (s, 1H), 7.6 (bs, 1H).

2.2.27.1-Methyl-3-(2-chloroethyl)-6,7-dimethoxyquinazoline-2,4-dione (45). Methyl 4,5-dimethoxy-2-(methylamino)-benzoate **44** (0.47 g, 2 mmol) and 2-chloroethylisocyanate (0.21 mL, 2.4 mmol) were heated to reflux for 48 h in toluene (50 mL) to yield 0.33 g of **45**. ^{1}H NMR ($CDCl_3$): δ (3.6 (s, 3H), 3.8 (t, 2H), 3.92 (s, 3H), 4.02 (s, 3H), 4.48 (t, 2H), 6.6 (s, 1H), 7.6 (s, 1H).

2.2.28. 3-[2-[(3aR,9bR)-*cis*-2,3,3a,4,5,9b-Hexahydro-6-methoxy-[1H]-benz[*e*]isoindol-2-yl]ethyl]-6,7-dimethoxy-1-methylquinazoline-2,4(1H,3H)-dione, Monohydrochloride (46). The benz[*e*]isoindole **5a** (0.2 g, 1 mmol), compound

45 (0.3 g, 1.05 mmol), and diisopropylethylamine (0.8 mL) were combined in acetonitrile (3 mL) and heated at reflux for 18 h. Solvents were removed in vacuo, and the residue was chromatographed on silica gel (18:1:1 EtOAc/H_2O/HCOOH) to yield 0.23 g (64%) of **46** as its formic acid salt that was converted to the HCl salt, mp 188−190 °C. ^{1}H NMR (free base): δ 1.52 (m, 1H), 1.75 (m, 1H), 2.28 (m, 2H), 2.48−2.87 (m, 5H), 3.42 (m, 3H), 3.6 (s, 3H), 3.81 (s, 3H), 3.95 (s, 3H), 4.02 (s, 3H), 4.25 (t, 2H), 6.58 (s, 1H), 6.66 (d, 1H), 6.78 (d, 1H), 7.1 (t, 1H), 7.61 (s, 1H). MS (DCI/NH_3): *m/e* 466 $(M + H)^+$. Anal. ($C_{25}H_{29}N_3O_5$·HCl·H_2O) C, H, N.

2.2.29. Ethyl 2-(*N*,*N*-dimethyl-*N*′-formamidinyl)-4,5-dimethoxybenzoate (47). Ethyl 6-amino-3,4-dimethoxybenzoate (5.2 g, 23.1 mmol) and *N*,*N*-dimethylformamide dimethylacetal (6.87 g, 57.7 mmol) were treated by the method of Gupton[36] to yield 6.7 g of **47**. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3H), 3.1 (s, 6H), 3.9 (s, 6H), 4.28 (q, 2H), 6.4 (s, 1H), 7.26 (s, 1H), 7. 36 (s, 1H).

2.2.30. 3-[2-[(3aR,9bR)-*cis*-2,3,3a,4,5,9b-Hexahydro-6-methoxy-[1H]-benz[*e*]isoindol-2-yl]ethyl]-6,7-dimethoxyquinazolin-4(3H)-one, Dihydrochloride (48). The compound **47** (2.5 g, 8.9 mmol) and the amine **6a** (0.57 g, 2.3 mmol) were refluxed in 1,4-dioxane (30 mL) with *p*-toluenesulfonic acid monohydrate (0.15 g, 0.8 mmol) for 4 h. The reaction mixture was concentrated to a crude oil, which was crystallized from MeOH to give **48** as the free base. The free base was converted to the HCl salt (0.67 g, 57%), mp 181−185 °C (EtOH/Et_2O). ^{1}H NMR (D_2O): δ 1.65 (m, 1H), 1.94 (m, 1H), 2.55 (m, 1H), 2.85 (m, 3H), 3.7 (m, 3H), 3.84 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.45 (t, 2H), 4.72 (m, 3H), 6.87 (d, 1H), 6.94 (d, 1H), 7.14 (s, 1H), 7.25 (t, 1H), 7.5 (s, 1H), 8.26 (s, 1H). MS (DCI/NH_3): *m/e* 436 $(M + H)^+$. $[\alpha]_D$ +27.4° (*c* 0.53, CH_3-OH). Anal. ($C_{25}H_{29}N_3O_4$·2HCl·1.5H_2O) C, H, N.

2.2.31. 3-[2-[(3aR,9bR)-*cis*-2,3,3a,4,5,9b-Hexahydro-6-methoxy-[1H]-benz[*e*]isoindol-2-yl)ethyl]-2,3-dihydro-6,7-dimethoxyquinazolin-4(1H)-one, Dihydrochloride (49). Compound **48** (0.15 g, 0.3 mmol) in MeOH (25 mL) was hydrogenated at 4 atm of H_2 at room temperature over 10% Pd/C catalyst (dry, 0.02 g) for 17 h. The catalyst was removed by filtration, and the filtrate was concentrated. The obtained residue was basified with K_2CO_3 to pH 13 and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated to give, after chromatography on silica gel (10% EtOAc/EtOH), the formic acid salt of **49** (0.06 g), which was converted to the HCl salt, mp 191−193 °C. ^{1}H NMR (CD_3-OD): δ 1.65 (m,1H), 1.95 (m, 1H), 2.6 (m, 1H), 2.8 (m, 2H), 2.95 (m, 1H), 3.05 (m, 2H), 3.4 (m, 2H), 3.65 (m, 1H), 3.8 (s, 3H), 4.05 (s, 3H), 4.12 (m, 2H), 4.2 (s, 3H), 4.6 (m, 2H), 6.8 (m, 2H), 7.08 (d, 1H), 7.18 (s, 1H), 7.8 (s, 1H). MS (DCI/NH_3): *m/e* 438 $(M + H)^+$. Anal. ($C_{25}H_{31}N_3O_4$·2 HCl·2.25H_2O) C, H, N.

2.2.32. *N*-[(4,5-Dimethoxy-2-nitrophenyl)methyl]-2,3,-3a,4,5,9b-hexahydro-6-methoxy-1H-benz[*e*]isoindole-2-ethaneamine (50). 4,5-Dimethoxy-2-nitrobenzaldehyde (0.68 g, 3.25 mmol) and the amine **6** (0.8 g, 3.25 mmol) in MeOH (100 mL) were treated with $NaBH_4$ (0.16 g, 4.23 mmol) at room temperature for 2 h by the method of Takai[37] to yield, after standard workup, 1.62 g of **43**. ^{1}H NMR ($CDCl_3$): δ 1.52 (m,-1H), 1.72 (m, 1H), 2.28 (t, 2H), 2.55 (m, 3H), 2.65 (m, 2H), 2.69 (m, 2H), 3.26 (m, 2H), 3.4 (m, 1H), 3.8 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 4.08 (s, 2H), 6.7 (m, 2H), 7.1 (t, 1H), 7.15 (s, 1H), 7.52 (s, 1H). MS (DCI/NH_3): *m/e* 442 $(M + H)^+$.

2.2.33. *N*-[(2-Amino-4,5-dimethoxyphenyl)methyl]-2,3,-3a,4,5,9b-hexahydro-6-methoxy-1H-benz[*e*]isoindole-2-ethaneamine (51). Compound **50** (1.62 g, 3.8 mmol) in MeOH (200 mL) was hydrogenated at 4 atm of H_2 over 0.7 g of Pd/C at room temperature for 4 h. The catalyst was filtered off and the filtrate evaporated to yield 1.2 g of **51**. ^{1}H NMR ($CDCl_3$): δ 1.55 (m, 1H), 1.73 (m, 1H), 2.2 (m, 2H), 2.6 (m, 5H), 2.76 (m, 2H), 3.27 (m, 2H), 3.4 (m, 1H), 3.73 (s, 2H), 3.74 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 6.28 (s, 1H), 6.67 (m, 2H), 7.02 (d, 1H), 7.27 (s, 1H).

2.2.34. 3-[2-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxyquinazoline, Dihydrochloride (52). To a solution of the compound **51** (0.3 g, 0.73 mmol) in EtOH (10 mL) was added 37% formaldehyde (0.4 mL) and concentrated HCl (0.4 mL). The reaction mixture was stirred at room temperature overnight. The solvents were evaporated, and the obtained residue was chromatographed on silica gel, eluting with 89: 9:1 CH_2Cl_2/MeOH/NH_4OH to yield 0.33 g of **52** as a free base, which was converted to the HCl salt, mp 152−154 °C. ^{1}H NMR (CD_3OD): δ 1.74 (m, 1H), 1.92 (m, 1H), 2.72 (m, 6H), 2.85 (m, 2H), 3.42 (m, 1H), 3.7 (m, 3H), 3.78 (s, 3H), 3.8 (s, 3H), 3.82 (s, 3H), 4.32 (s, 2H), 4.6 (bs, 2H), 6.62 (s, 1H), 6.78 (m, 3H), 7.1 (d, 1H). MS (DCI/NH_3): *m/e* 424 $(M + H)^+$. Anal. ($C_{25}H_{33}N_3O_3$·2HCl·2.25H_2O) C, H, N.

2.2.35. 3-[2-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-2-yl)ethyl]-3,4-dihydro-6,7-dimethoxyquinazolin-2(1H)-one, Dihydrochloride (53). Compound **51** (0.3 g, 0.73 mmol) in CH_3CN (10 mL) was treated with 1,1′-carbonyldiimidazole (0.15 g, 0.82 mmol) for 3 h at room temperature by the method of Takai[37] to yield **53** (0.25 g) after removal of the solvent and conversion to HCl salt, mp 175−177 °C (MeOH/Et_2O). ^{1}H NMR (CD_3OD): δ 1.58 (m, 1H), 1.76 (m, 1H), 2.38−2.7 (m, 6H), 2.9 (m, 2H), 3.42 (m, 1H), 3.58 (m, 3H), 3.72 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 4.43 (s, 2H), 6.42 (s, 1H), 6.68 (m, 3H), 7.0 (d, 1H). MS (DCI/NH_3): *m/e* 438 $(M + H)^+$. Anal. ($C_{25}H_{31}N_3O_4$·2 HCl·0.75H_2O) C, H, N.

2.2.36. 2-(2-Chloroethyl)-2,3,3a,4,5,9b-hexahydro-6-methoxy-1H-benz[*e*]isoindole (54). To a solution of the hydrochloride salt of benz[*e*]isoindole **5** (1.0 g, 4.17 mmol) and 1-bromo-2-chloroethane (0.72 g, 5.0 mmol) in DMF (25 mL) was added potassium carbonate (1.27 g, 9.7 mmol), and the reaction mixture was stirred at room temperature overnight. The precipitate was filtered off, and the filtrate was acidified. Upon addition of ether a precipitate was formed that was filtered off and crystallyzed from EtOH/ether to yield 1.3 g of **54** as an off-white precipitate. ^{1}H NMR ($CDCl_3$): δ 1.52 (m, 1H), 1.75 (m, 1H), 1.8 (m, 1H), 2.21 (m, 1H), 2.4−2.8 (m, 4H), 2.82 (m, 1H), 3.4 (m, 3H), 3.7 (m, 1H), 3.8 (s, 3H), 3.9 (m, 1H), 4.3 (m, 1H), 6.72 (m, 2H), 7.12 (m, 1H).

2.2.37. 2-[2-[(3aR,9bR)-*cis*-2,3,3a,4,5,9b-Hexahydro-6-methoxy-[1H]-benz[*e*]isoindol-2-yl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, Dihydrochloride (55). Potassium carbonate (0.12 g, 0.87 mmol) was added to a solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.1 g, 0.44 mmol) and compound **55** (0.11 g, 0.36 mmol) in DMF (5 mL), and the reaction mixture was stirred at room temperature overnight. Solids were filtered off, the filtrate was evaporated, and the residue was partitioned in EtOAc/$NaHCO_3$. The organic layer was washed with H_2O and then brine, dried (Na_2SO_4), and evaporated. The obtained residue was chromatographed, eluting with 2% MeOH/CH_2Cl_2 to give 0.13 g of **55** as a free base, which was converted to the HCl salt, mp >200 °C. ^{1}H NMR ($CDCl_3$) (free base): δ 1.65 (m, 1H), 1.9 (m, 1H), 2.6 (m, 1H), 2.9 (m, 3H), 3.13 (m, 2H), 3.6 (m, 3H), 3.75 (s, 3H), 3.8 (s, 6H), 6.76 (s, 1H), 6.8 (m, 2H), 6.82 (s, 1H), 7.18 (t, 1H). MS (DCI/NH_3): *m/e* 452 $(M + H)^+$. Anal. ($C_{26}H_{34}N_2O_3$·2HCl·0.2H_2O) C, H, N.

2.2.38. 2-[2-[(3aR,9bR)-*cis*-2,3,3a,4,5,9b-Hexahydro-6-methoxy-[1H]-benz[*e*]isoindol-2-yl)ethyl]-3,4-dihydro-6,7-dimethoxyisoquinolin-1(2H)-one, Monohydrochloride (56). The isocyanate (2.7 g, 13.1 mmol) obtained from 3,4-dimethoxyphenethylamine was treated with $POCl_3$ and $SnCl_4$ by the method of Y. Tsuda[38] to yield 1.36 g of the intermediate 6,7-dimethoxy-3,4-dihydroisoquinoline-1-one. ^{1}H NMR (CDCl3): δ 2.9 (m, 2H), 3.55 (m, 2H), 3.9 (s, 6H), (m, 6.68 (s, 1H), 6.8 (s, 1H), 6.82 (s, 1H), 7.58 (s, 1H).

6,7-Dimethoxy-3,4-dihydroisoquinoline-1-one (0.5 g, 2.42 mmol) was dissolved in DMF, and NaH (0.11 g, 4.84 mmol) was added to the solution. After the mixture was stirred for 30 min at room temperature, compound **54** (0.77 g, 2.89 mmol) was added to the solution. The reaction mixture was heated at 40 °C overnight, then diluted with H_2O and extracted with Et_2O (2×). The organic layer was washed with $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and evaporated to yield, after chromatography on silica gel, **56** as a free base, which was converted to the HCl salt, mp >200 °C. ^{1}H NMR ($CDCl_3$) (free

base): δ 1.54 (m, 1H), 1.75 (m, 3H), 2.35 (m, 2H), 2.57 (m, 1H), 2.72 (m, 8H), 2.88 (m, 3H), 3.6 (s, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 6.5 (s, 1H), 6.59 (s, 1H), 6.69 (d, 1H), 6.75 (d, 1H), 7.1 (t, 1H), 7.58 (s, 1H). MS (DCI/NH_3): *m/e* 437 $(M + H)^+$. Anal. ($C_{26}H_{32}N_2O_4 \cdot HCl \cdot 1.5H_2O$) C, H, N.

2.2.39. 2-Amino-*N*-[2-[(3aR,9bR)-*cis*-2,3,3a,4,5,9b-hexahydro-6-methoxy-[1H]-benz[*e*]isoindol-2-yl]ethyl]-4,5-dimethoxybenzamide, Dihydrochloride (57). To a solution of the amine **6** (0.25 g, 1.01 mmol), 2-amino-4,5-dimethoxybenzoic acid (0.22 g, 1.12 mmol), diisopropylethylamine (0.3 mL), and HOBT (0.21 g, 1.53 mmol) in a 1:1 mixture of CH_2Cl_2 and DMF was added EDCI (0.29 g, 1.53 mmol). The reaction mixture was stirred at room temperature overnight and after standard workup yielded **57**, mp 193−195 °C. ^{1}H NMR (CD_3OD): δ 1.7 (m, 1H), 1.93 (m, 1H), 2.6 (m, 2H), 2.85 (m, 4H), 3.08 (m, 2H), 3.5 (m, 2H), 3.78 (m, 2H), 3.82 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 6.8 (d, 1H), 6.82 (d, 1H), 6.9 (s, 1H), 7.18 (t, 1H), 7.5 (s, 1H). MS (DCI/NH_3): *m/e* 426 $(M + H)^+$. Anal. ($C_{24}H_{31}N_3O_4 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

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