Structure−Activity Relationships of a Series of Substituted Benzamides: Potent D_2/5-HT_2 Antagonists and 5-HT_{1a} Agonists as Neuroleptic Agents

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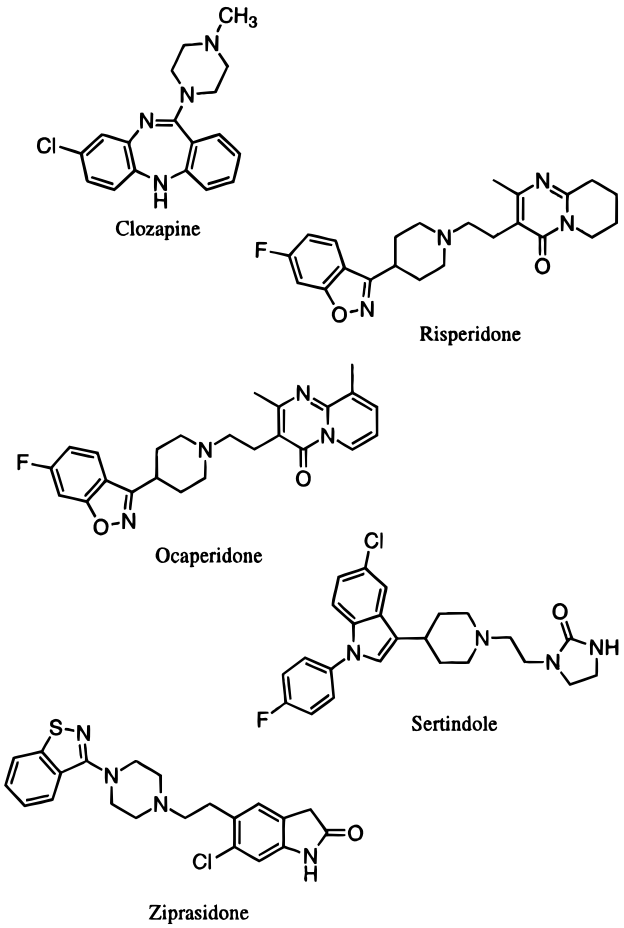
A series of substituted (4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide derivatives was prepared and evaluated as potential atypical antipsychotic agents. The target compounds were readily prepared from their benzoyl chloride, benzoic acid, or isatoic anhydride precursors, and they were evaluated *in vitro* for their ability to bind to dopamine D_2, serotonin 5-HT_2, and serotonin 5-HT_{1a} receptors. To assess the potential antipsychotic activity of these compounds, we investigated their ability to inhibit the apomorphine-induced climbing response in mice. Selected compounds were evaluated further to determine their side-effect potentials. Structure−activity relationships of both mono- and polysubstituted benzamides are discussed herein. While several analogues had potent *in vitro* and *in vivo* activities indicative of potential atypical antipsychotic activity, anthranilamide **77** (1192U90) demonstrated a superior pharmacological profile. As a result of this investigation, 1192U90 (2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride) was selected for further evaluation and is currently in phase I clinical trials as a potential atypical antipsychotic agent.

Introduction

Owing to its superior atypical antipsychotic profile, clozapine has become the standard therapy to which all new antipsychotic agents are compared. Clozapine is an effective antipsychotic agent that is nearly devoid of the extrapyramidal side effects (EPS) that often accompany typical antipsychotic agents such as haloperidol.[1−4] Its therapeutic use has been restricted, however, because a potentially fatal blood dyscrasia, agranulocytosis, develops in some individuals who use clozapine.[5−7] Over the past 2 decades, many neuroleptic agents have been investigated in attempts to identify a compound that retains a clozapine-like antipsychotic profile without this serious side effect. Of the several theories that have been advanced to explain clozapine's atypical antipsychotic profile, the mixed dopamine D_2/serotonin 5-HT_2 hypothesis has been the subject of most recent investigations.[8−19] For example, compounds such as risperidone,[9] ocaperidone,[10] sertindole,[11] and ziprasidone[12] are mixed D_2/5-HT_2 antagonists at various stages of investigation.

We recently described the potential antipsychotic activity associated with a series of cyclic benzamides **1** possessing mixed dopamine and serotonin antagonist activity.[19] These derivatives antagonize serotonin 5-HT_2 receptors more potently than dopamine D_2 receptors, indicating that they may act as atypical antipsychotic agents. In addition, several of these derivatives were shown to be serotonin 5-HT_{1a} receptor agonists, an activity that may help to reduce the occurrence of EPS and help relieve the anxiety that can often trigger psychotic episodes. During the development of this series, we also evaluated a few intermediate benzamides (**2**) where the amide was not restricted by a covalent bond to the *ortho* position of the aromatic ring. These noncyclic derivatives exhibited potent *in vitro* and *in vivo* activities, which suggested they would be effective against both the positive and negative symptoms of schizophrenia while inducing fewer EPS than typical antipsychotic agents. We subsequently extended our structure−activity relationship (SAR) investigations by examining the potential antipsychotic activity of a series of substituted *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piper-

Chart 1



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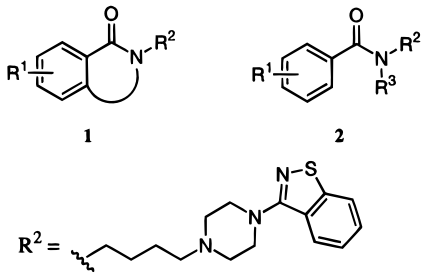
azinyl)butyl)benzamides. In this paper, we report the synthesis and biological evaluation of substituted benzamides with the general structure **2**. These investigations have resulted in the identification of a clinical candidate antipsychotic agent, 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride (**77**, 1192U90).



1 **2**

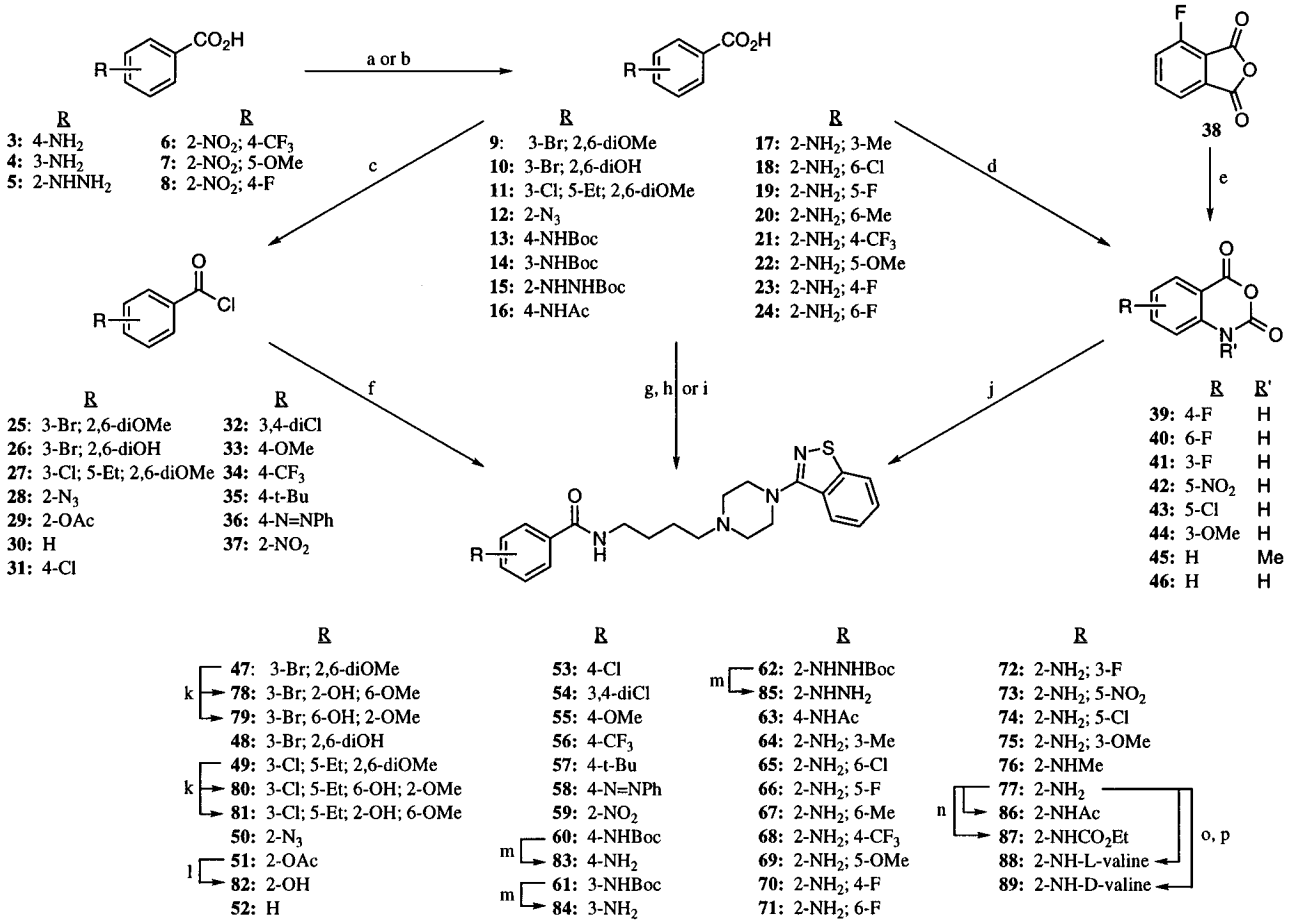
Chemistry

Several synthetic routes were examined for assembling the desired substituted benzamides from their benzoyl chloride, benzoic acid, and isatoic anhydride precursors. The methods used to prepare the appropriate intermediates and the five general approaches employed to obtain the target compounds are summarized in Scheme 1. The appropriately substituted benzoic acid precursors required for the preparation of a majority of the benzamide derivatives were prepared as follows. Treatment of amino- and hydrazinobenzoic acids **3**−**5** with di-*tert*-butyl dicarbonate in 1,4-dioxane provided the corresponding carbonate-protected derivatives **13**−**15**. Substituted anthranilic acids **21**−**23** were obtained by the catalytic hydrogenation of *o*-nitrobenzoic acids **6**−**8**, respectively. Polysubstituted benzoic acids **9**−**11** were prepared by literature procedures,[20,21] and 2-azidobenzoic acid (**12**) was obtained via a Sandmeyer reaction using anthranilic acid and sodium azide.[22] Anthranilic acids **16**−**20** and **24** were obtained from commercial suppliers.

The first general approach, which provided target benzamides **47**−**59**, involved the condensation of substituted benzoyl chlorides **25**−**37** with 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole.[23] The requisite benzoyl chlorides were either commercially available (compounds **29**−**37**) or prepared by treatment of their corresponding benzoic acids with thionyl chloride in toluene (compounds **25**−**28**).

The next three general methods employed the appropriately substituted benzoic and anthranilic acids directly. Reaction of benzoic acids **13**−**16** with isobutyl chloroformate followed by treatment of the resulting mixed anhydrides with 3-(4-(4-aminobutyl)-1-piperazi-

Scheme 1[a]



[a] Reagents: (a) $O(CO_2t\text{-}Bu)_2$, 1,4-dioxane, 5% Na_2CO_3, 0−25 °C; (b) H_2, 5% Pd/C; (c) $SOCl_2$, DMF, toluene, 65−85 °C; (d) $ClCO_2CCl_3$, 1,4-dioxane, reflux; (e) N_3SiMe_3, $CHCl_3$; (f) 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, Et_3N, CH_2Cl_2 or $CHCl_3$, 0−25 °C; (g) $ClCO_2i$-Bu, THF, Et_3N, 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, −35−25 °C; (h) $SiCl_4$, pyridine, 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, 145 °C; (i) dicyclohexylcarbodiimide, 1-hydroxybenzotriazole, 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, DMF, 0−25 °C; (j) 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, EtOH or THF, 25 °C; (k) BBr_3, CH_2Cl_2, 1 N ethereal HCl, 25 °C; (1) MeOH, NaOMe, 25 °C; (m) F_3CCO_2H, anisole, $CHCl_3$, 25 °C; (n) MeCOCl or $ClCO_2Et$, Et_3N, CH_2Cl_2 or $CHCl_3$, 0−25 °C; (o) *N*-((9*H*-fluoren-9-ylmethoxy)carbonyl)-L(or D)-valyl chloride,[28] $CHCl_3$, Na_2CO_3, 25 °C; (p) 4-(aminomethyl)piperidine, 25 °C.

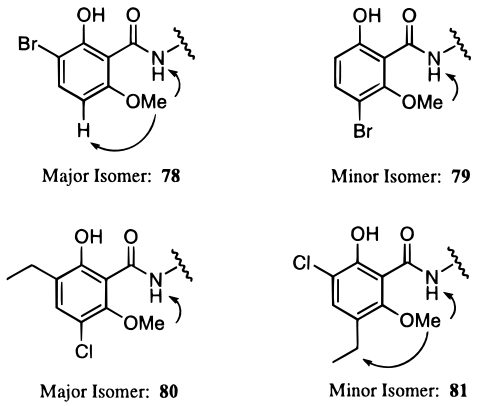


Figure 1. Significant NOE signals observed upon irradiation of the *o*-methoxy groups of salicylamides **78**−**81**.

nyl)-1,2-benzisothiazole provided target benzamides **60**−**63**. Alternatively, azidobenzamide **50** was obtained from a dicyclohexylcarbodiimide coupling of the primary amine with *o*-azidobenzoic acid (**12**). Anthranilic acids **17**−**22** were effectively condensed with the primary amine by employing silicon tetrachloride as a coupling reagent as described by Chan[24] and Kornet[25] to give anthranilamides **64**−**69**, respectively. To obtain optimum yields in the silicon tetrachloride-mediated reactions, it was necessary to employ rigorously dried pyridine as the solvent.

The final general method outlined in Scheme 1 involved the condensation of the primary amine with an appropriately substituted isatoic anhydride. This procedure produced anthranilamides **70**−**77** and represented an alternative to the silicon tetrachloride coupling method. The necessary isatoic anhydrides were commercially available or synthesized by one of two methods. Reaction of substituted anthranilic acids **23** and **24** with trichloromethyl chloroformate gave the corresponding 4- and 6-fluorinated isatoic anhydrides **39** and **40**, respectively. Alternatively, a 40:60 mixture of the 6-fluoro- (**40**) and the 3-fluoro- (**41**) isatoic anhydride was obtained upon the treatment of 3-fluorophthalic anhydride (**38**) with azidotrimethylsilane in anhydrous chloroform. This method of isatoic anhydride synthesis has been studied by Washburne and coworkers and involves the overall insertion of an NH moiety between the carbonyl and the aryl group of the anhydride.[26] The target anthranilamides **70**−**77** were prepared in yields ranging from 43% to 65% by the reaction of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole with isatoic anhydrides **39**−**46**. In some cases, a small amount of the ethyl 2-aminobenzoate was obtained in these reactions. This byproduct results from the addition of ethanol to the isatoic anhydride and can be avoided by the use of tetrahydrofuran rather than ethanol as the solvent.

With benzamides **47**−**77** in hand, further functional group manipulations allowed for the preparation of several additional analogues. For example, monodemethylation of dimethoxy derivatives **47** and **49** with boron tribromide provided isomeric mixtures of *o*-hydroxybenzamides **78**/**79** and **80**/**81**, respectively. These isomers were separated by flash chromatography, and the regiochemistry was determined by a series of NOE experiments. The NOE signals observed from irradiation of the *o*-methoxy substituents of each isomer are illustrated in Figure 1. The major isomer resulting from the demethylation of dimethoxy benzamide **47** was assigned to be the 2-hydroxy derivative **78** due to the NOE of the adjacent aromatic proton. Analogously, the minor product in the demethylation of the tetrasubstituted benzamide **49** was shown to be the 2-hydroxy isomer **81** by enhancement of the methylene of the 5-ethyl group. In each case, the more sterically hindered methyl group preferentially reacted with boron tribromide. These results are consistent with those reported by de Paulis *et al*. for the preparation of 6-methoxysalicylamides.[21,27]

Salicylamide **82** was obtained by the basic hydrolysis of the corresponding acetate **51**. Deprotection of *tert*-butyl carbamates **60**−**62** was effected by treatment with trifluoroacetic acid in chloroform to provide amino and hydrazino analogues **83**−**85**, respectively. The final derivatives outlined in Scheme 1 (compounds **86**−**89**) were derived from the acylation of *o*-aminobenzamide **77**. Reaction of **77** with either acetyl chloride or ethyl chloroformate provided amide **86** and carbamate **87**, while L- and D-valinamides **88** and **89** were prepared by the condensation of benzamide **77** with *N*-((9*H*-fluoren-9-ylmethoxy)carbonyl)-L(or D)-valyl chloride followed by the deprotection of the FMOC protecting group with 4-(aminomethyl)piperidine.[28] Mosher amides of both **88** and **89** were prepared to assess their optical purity. Examination of these derivatives by both HPLC and ^{19}F NMR techniques indicated that the valyl amides were pure enantiomers and that no epimerization occurred in the synthetic process.

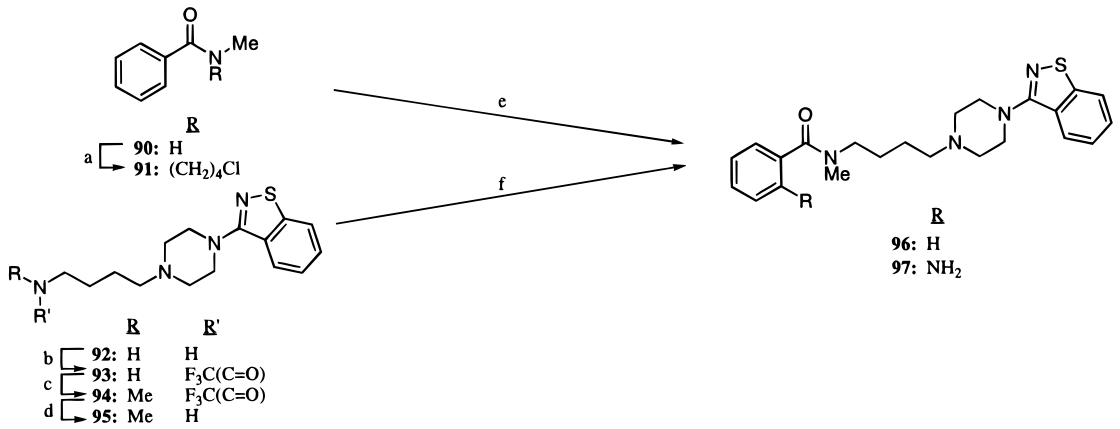
The syntheses of the final two benzamide derivatives (**96** and **97**) are outlined in Scheme 2. Alkylation of the sodium salt of *N*-methylbenzamide (**90**) with 1-bromo-4-chlorobutane in dimethylformamide, followed by displacement of the resulting chloride **91** with 3-(1-piperazinyl)-1,2-benzisothiazole,[23] gave benzamide **96**. An alternative route was required to prepare the analogous *N*-methylanthranilamide derivative **97**. Treatment of primary amine **92** with trifluoroacetic anhydride provided amide **93** in 86% yield. Alkylation of **93** with methyl iodide followed by hydrolysis of trifluoroacetamide **94** gave amine **95**. The anthranilamide target, **97**, was obtained by the condensation of **95** with isatoic anhydride in ethanol.

Results and Discussion

In the first phase of this investigation, it was necessary to select a set of substituents that would provide the greatest structural diversity within a limited number of compounds. To accomplish this, we based our initial substituent selection on a cluster analysis strategy described by Hansch and co-workers.[29] In this approach, substituents are divided into subgroups (clusters) based on various physicochemical parameters using combinations of lipophilic, electronic, molar refractivity, molecular weight, and Swain and Lupton-type constants. The cluster set that incorporated the broadest set of parameters was employed in our investigation. We prepared a series of monosubstituted benzamides that included representatives from several different clusters designed to maximize the difference in substituent properties.

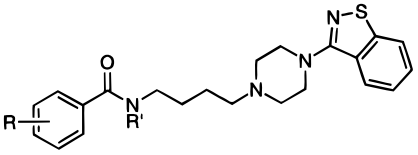
The substituted benzamides were evaluated in *in vitro* receptor binding assays at dopamine D_2 and serotonin 5-HT_{1a} and 5-HT_2 receptors.[19,32] As a preliminary

Scheme 2[a]



[a] Reagents: (a) NaH, DMF, $Br(CH_2)_4Cl$, 0 °C; (b) TFAA, CH_2Cl_2, 0 °C; (c) NaH, DMF, MeI, 0−25 °C; (d) K_2CO_3, MeOH, H_2O, 25 °C; (e) 3-(1-piperazinyl)-1,2-benzisothiazole,[23] MeCN, Et_3N, reflux; (f) isatoic anhydride, EtOH, 25 °C.

Table 1. *In Vitro* and *in Vivo* Biological Activities of Reference Standards and Monosubstituted Benzamides



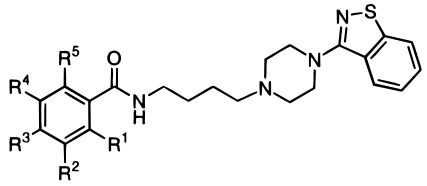
				receptor binding[c] IC_{50} (nM)				antagonism of apomorphine-induced mouse climbing[e] ED_{50} (mg/kg)	
compd no.[a]	R	R′	cluster[b]	D_2	5-HT_{1a}	5-HT_2	D_2/5-HT_2[d]	ip	po
50	2-N_3	H	3	19	3.7	1.8	10	25	
52	H	H	1	26	5.2	2.1	12	1.1	21.5
53	4-Cl	H	3	57	15	5.6	10	9.4	>25
55	4-OMe	H	5	34	9.0	2.3	15	2.4	>25
56	4-CF_3	H	6	27	9.1	1.5	18	12.5	>25
57	4-*t*-Bu	H	9	340	520	68	5	5.1	>25
58	4-N=NPh	H	8	230	540	26	9	>25	
59	2-NO_2	H	3	14	6.4	3.7	4	25	
60	4-NHBoc	H	*f*	14	0.70	0.23	61	>25	
61	3-NHBoc	H	*f*	4.4	12	1.3	3	>25	
63	4-NHAc	H	4	41	37	51	0.8	>25	>25
76	2-NHMe	H	5	4.7	10	12	0.4	5.8	15.6
77	2-NH_2	H	5	32	3.8	3.3	10	1.5[g]	10.1[h]
82	2-OH	H	5	5.8	12	3.9	1	1.0	21.5
83	4-NH_2	H	5	63	23	150	0.4	>25	
84	3-NH_2	H	5	66	6.6	2.6	25	25	
85	2-$NHNH_2$	H	5	32	3.8	2.4	13	10.8	40.4
86	2-NHAc	H	4	31	5.2	2.0	16	4.1	22.3
87	2-$NHCO_2Et$	H	7	5.4	5.6	1.4	4	1.8	32.8
88	2-NH-L-valine	H	*f*	21	5.4	2.7	8	2.6	17.9
89	2-NH-D-valine	H	*f*	4.3	8.4	1.6	3	>25	
96	H	Me	1	17	1.4	3.9	4	10.0	22.4
97	2-NH_2	Me	5	34	1.2	2.3	15	>12	
haloperidol				40	7000	360	0.01	1.8	0.5
clozapine				290	2000	28	10	26.2[i]	22.5[j]

[a] Hydrochloride salts. [b] Cluster set 1 (group 10) as defined by Hansch *et al.*[29] [c] D_2, [^{3}H]raclopride binding; 5-HT_{1a}, [^{3}H]-8-OH-DPAT binding; 5-HT_2, [^{3}H]ketanserin binding. [d] Ratio of dopamine D_2 (IC_{50}) to serotonin 5-HT_2 (IC_{50}) receptor binding. [e] For experimental protocol, see ref 19. [f] This substituent was not included in the cluster analysis reported by Hansch *et al.*[29] [g] 95% confidence limits = 0.7−4.2 mg/kg. [h] 95% confidence limits = 5.2−19.3 mg/kg. [i] 95% confidence limits = 9.4−73.2 mg/kg. [j] 95% confidence limits = 12.8−39.8 mg/kg.

antipsychotic assay, the compounds were evaluated *in vivo* for their ability to antagonize the apopmorphine-induced climbing response in mice.[33] The biological activities of the monosubstituted benzamides and two standards, haloperidol and clozapine, are summarized in Table 1. Also included in Table 1 are the calculated D_2/5-HT_2 receptor binding ratios. Neuroleptic agents with D_2/5-HT_2 ratios > 1 have been postulated to exhibit an atypical antipsychotic profile.[8]

The clusters for the initial compounds studied are indicated in Table 1. Nonsubstituted benzamide **52**, representing cluster 1, exhibited potent receptor binding and possessed a good D_2/5-HT_2 ratio of 12. This derivative was also very potent in the mouse climbing assay when administered ip. The corresponding tertiary amide **96** showed similar potency *in vitro* but reduced activity when administered ip and comparable activity when given orally. Compounds from cluster 3 (**50**, **53**,

Table 2. *In Vitro* and *in Vivo* Biological Activities of Polysubstituted Benzamides



						receptor binding[b] IC_{50} (nM)				antagonism of apomorphine-induced mouse climbing[d] ED_{50} (mg/kg)	
compd no.[a]	R^1	R^2	R^3	R^4	R^5	D_2	5-HT_{1a}	5-HT_2	D_2/5-HT_2[c]	ip	po
47	OMe	Br	H	H	OMe	13	74	12	1	>25	
48	OH	Br	H	H	OH	1.0	120	16	0.06	6.0	28.8
49	OMe	Cl	H	Et	OMe	58	180	30	2	26	
54	H	Cl	H	Cl	H	100	49	1.7	58	>25	
64	NH_2	Me	H	H	H	4.0	4.0	5.8	0.7	5.4	37.6
65	NH_2	H	H	H	Cl	38	38	3.4	11	>25	
66	NH_2	H	H	F	H	3.0	3.0	2.3	1	2.2	31.8
67	NH_2	H	H	H	Me	290	64	8.9	32	>25	
68	NH_2	H	CF_3	H	H	18	12	2.3	8	6.9	>50
69	NH_2	H	H	OMe	H	35	10	1.4	25	2.1	>50
70	NH_2	H	F	H	H	15	4.2	0.59	25	2.5	27.1
71	NH_2	H	H	H	F	15	4.2	1.6	0.9	7.8	20.8
72	NH_2	F	H	H	H	13	1.5	0.50	26	0.9	14.3
73	NH_2	H	H	NO_2	H	13	20	3.8	3	19.6	
74	NH_2	H	H	Cl	H	13	9.4	1.6	8	<6	25
75	NH_2	OMe	H	H	H	7.8	4.1	1.6	5	2.2	20.3
78	OH	Br	H	H	OMe	0.62	26	15	0.04	1.5	14.3
79	OMe	Br	H	H	OH	30	33	14	2	4.7	>25
80	OMe	Cl	H	Et	OH	80	69	6.8	12	>25	
81	OH	Cl	H	Et	OMe	11	23	6.3	2	25.5	

[a] Hydrochloride salts. [b] D_2, [^{3}H]raclopride binding; 5-HT_{1a}, [^{3}H]-8-OH-DPAT binding; 5-HT_2, [^{3}H]ketanserin binding. [c] Ratio of dopamine D_2 (IC_{50}) to serotonin 5-HT_2 (IC_{50}) receptor binding. [d] For experimental protocol, see ref 19.

and **59**) showed good receptor binding affinities, but only the 4-chloro derivative **53** exhibited good *in vivo* activity (ip). The two compounds contained in the fourth cluster were NHAc regioisomers, benzamides **63** and **86**. From the examination of activity of these two derivatives, it was clear that not only the type of substituent but also the position of substitution was critical to activity. The 4-substituted derivative **63** showed both poor D_2/5-HT_2 selectivity and *in vivo* activity, while the opposite was true of the 2-substituted isomer **86**. This dependence on the position of the substituent relative to the amide carbonyl was also observed in cluster 5 with amino substitutions (compounds **77**, **83**, and **84**). As in the case of the NHAc derivatives, the *ortho* isomer provided the best results. Anthranilamide **77** displayed high affinities for all of the targeted receptors and a D_2/5-HT_2 ratio comparable to that of clozapine. This derivative potently antagonized the apomorphine-induced climbing response in mice, both by ip and po administration, with ED_{50}'s of 1.5 and 10.1 mg/kg, respectively. The *o*-hydrazino derivative **85** exhibited a similar receptor binding profile to **77** but had reduced *in vivo* activity. Replacing the amino group of **77** with a hydroxyl group gave salicylamide **82**, which possessed a less desirable D_2/5-HT_2 selectivity. (Trifluoromethyl)benzamide **56** of cluster 6 showed good affinity and selectivity *in vitro* but poor oral bioavailability, while ethyl carbamate **87** of cluster 7 retained oral activity. If the alkyl groups of the carbamate derivatives play a minor role, then a similar positional preference for the *ortho* position may also be present within this series when *in vivo* activity is examined, **87** vs **60** and **61**. The final two clusters contain relatively large substituents and are represented by the *tert*-butyl- and (phenylazo)benzamides **57** and **58**, respectively. These sterically encumbered derivatives exhibited weaker binding affinities to all of the targeted receptors.

Selection of the initial substituents based on the Hansch cluster analysis strategy, although not an exhaustive study, allowed us to examine a broad range of derivatives. From this initial data set, it appeared that substituents from cluster 5 provided the best results. Perhaps a more important observation was that the biological activities of regioisomeric analogues were vastly different: Compounds with the substituent in the position *ortho* to the amide carbonyl demonstrated greater *in vivo* activity (*e.g.*, **77**). The excellent biological profile of the *o*-amino derivative **77** warranted further investigation. Methylation of the *o*-amino substituent resulted in a derivative with a poor D_2/5-HT_2 ratio (benzamide **76**), while *in vivo* activity was diminished when the amide nitrogen of **77** was methylated (tertiary amide **97**). Valinamide analogues **88** and **89** displayed decreased *in vivo* activities when administered po.

We examined polysubstituted benzamides in the second phase of these investigations (Table 2). Two main structural types are represented in Table 2, anthranilamide and salicylamide derivatives. In general, substitution of the anthranilamide ring was detrimental to oral activity (compounds **64**−**75**). Substitution was tolerated best at the position *ortho* to the amine substituent (*e.g.*, methyl derivatives **64** vs **67**, and methoxy derivatives **75** vs **69**). While fluorine was tolerated at all of the positions (R^{2-5}), the most potent derivative was again the analogue that was substituted

Table 3. Secondary Pharmacological Activities of Substituted Benzamide Derivatives and Reference Standards in Assays Indicating EPS Liability Potential (ip Data)

	antagonism of apomorphine-induced		
compd no.[a]	mouse climbing[b] ED_{50} (mg/kg, ip)	stereotypy (mouse)[b] ED_{50} (mg/kg, ip)	stereotypy[c] / climbing
72	0.9	8.9	10
76	5.8	13.5	2
77	1.5[d]	10.2[e]	7
78	1.5	15.4	10
88	2.6	26.9	7
haloperidol	1.8	0.4	0.2
clozapine	26.2[f]	136.1[g]	5

[a] Hydrochloride salts. [b] For experimental protocol, see ref 19. [c] Ratio of ED_{50} for antagonism of apomorphine-induced stereotypy to ED_{50} for antagonism of apomorphine-induced climbing. [d] 95% confidence limits = 0.7−4.2 mg/kg. [e] 95% confidence limits = 4.8−22.1 mg/kg. [f] 95% confidence limits = 9.4−73.2 mg/kg. [g] 95% confidence limits = 79.1−234.1 mg/kg.

ortho to the amine at R^2 (3-fluoroanthranilamide **72**). This derivative and the 4-fluoro analogue **70** displayed excellent D_2/5-HT_2 selectivities, while substitution with fluorine at R^4 and R^5 gave derivatives with low D_2/5-HT_2 ratios (compounds **66** and **71**, respectively).

The potent activity of salicylamide **82**, coupled with reports of other salicylamides studied by researchers at Astra pharmaceuticals,[21,27] led us to prepare derivatives **47**−**49** and **78**−**81**. The substitution patterns that we chose to examine paralleled those found in remoxipride and eticlopride derivatives. Remoxipride and eticlopride have been extensively studied and shown to be selective dopamine D_2 antagonists. In our series, the dimethoxybenzamide that contains the remoxipride substitution, compound **47**, showed poor *in vivo* activity. When the methyl of the methoxy group *ortho* to the bromine was removed, a significant increase in D_2 affinity was observed (salicylamides **48** and **78**). This result is consistent with that reported for the analogous remoxipride derivative (3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)-methyl)-2-hydroxy-6-methoxybenzamide, FLA-797).[27] Unfortunately, a corresponding increase in affinities to the 5-HT_2 receptor was not obtained, and poor D_2/5-HT_2 ratios resulted. The second polysubstituted salicylamide substitution patterns we investigated were related to eticlopride. These derivatives also provided disappointingly poor results in our series (compounds **49**, **80**, and **81**).

In the next phase of our investigation, several of the most potent derivatives were selected for further examination to assess their potential side-effect liability. Compounds that possessed ED_{50}'s of <20 mg/kg (po) in the mouse climbing assay were evaluated for their ability to inhibit apomorphine-induced stereotyped behavior in mice (ip and po) and for their ability to induce catalepsy in mice (po).[34] Inhibition of apomorphine-induced stereotypic behaviors indicates dopamine receptor antagonism in the extrapyramidal dopamine system, which is associated with the induction of motor side effects as seen with typical antipsychotic agents. The stereotypy-to-climbing and catalepsy-to-climbing ratios were calculated as measures of the compound's potential side-effect liability. The results from ip and po administration of compounds **72**, **76**−**78**, and **88** are reported in Tables 3 and 4, respectively. The appropriate data for antagonism of apomorphine-induced mouse climbing and data for the standards, haloperidol and clozapine, are also included for convenience. Examination of the ip data revealed that all of the benzamide derivatives exhibited therapeutic ratios equal to or greater than that of the typical antipsychotic haloperidol, while four of these analogues, **72**, **77**, **78**, and **88**, gave ratios superior to that observed for clozapine.

To narrow the field further, these derivatives were evaluated orally (Table 4). Anthranilamide **77** and salicylamide **78** exhibited excellent stereotypy/climbing ratios (2−6 times higher than those of the standards), while 3-fluoro anthranilamide **72**, *N*-methylanthranilamide **76**, and valinamide **88** were less selective. However, when the catalepsy/climbing ratios were compared, anthranilamide **77** continued to show a superior selectivity with a ratio of 19. When given orally, compound **77** exhibited therapeutic ratios *ca*. 2.5 times higher than those of haloperidol and clozapine.

On the basis of these initial results, anthranilamide **77** (1192U90) was chosen to be tested in a battery of pharmacological assays. These assays included additional neurochemical, behavioral, and electrophysiological evaluations and were designed to further evaluate the antipsychotic profile of 1192U90 and assess its potential side-effect liability. The details of these studies will be reported elsewhere; however, some of the biological highlights are summarized as follows. Neurochemical experiments indicated that 1192U90 bound potently at dopamine D_2, serotonin 5-HT_{1a}, serotonin 5-HT_2, and adrenergic α_1 and α_2 receptors.[35] In addition to its dopamine D_2 activity, 1192U90 has been shown to potently bind to the dopamine D_4 receptor,[36] a dopamine receptor subtype recently suggested to be important in the atypical antipsychotic profile of clozapine.[37] The results of 1192U90 in behavioral models in rats[38] and monkeys[39] qualitatively paralleled those results found in the mouse assays. In other words, 1192U90 antagonized behaviors elicited by dopamine D_2 receptor agonists (indicating potential antipsychotic activity) at lower doses than those required to antagonize behaviors reflecting EPS potential. In acute electrophysiology studies, 1192U90 was a potent dopamine D_2 receptor antagonist in the limbic and nigro-striatal dopamine systems as well as a serotonin 5-HT_{1a} receptor agonist.[35] In chronic electrophysiology studies, 1192U90 reduced the number of spontaneously firing neurons in the limbic dopamine system but not in the nigro-striatal dopamine system.[35] These results indicated that 1192U90 should have a low propensity to induce EPS.

Conclusions

Several mono- and polysubstituted benzamides were readily obtained from the reaction of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole with an appropriately substituted benzoic acid, benzoyl chloride, or isatoic anhydride precursor. Initial substituent selection was based on the method reported by Hansch and co-workers to obtain the most diverse set of derivatives. The compounds were evaluated in *in vitro* receptor binding assays at dopamine D_2 and serotonin 5-HT_{1a} and 5-HT_2 receptors and *in vivo* in the apomorphine-induced mouse climbing assay. Structure−activity relationships within the series of monosubstituted derivatives revealed a preference for an amino substituent *ortho* to the benzamide carbonyl (*i.e.*, anthranil-

Table 4. Secondary Pharmacological Activities of Substituted Benzamide Derivatives and Reference Standards in Assays Indicating EPS Liability Potential (po Data)

compd no.[a]	antagonism of apomorphine-induced mouse climbing[b] ED_{50} (mg/kg, po)	antagonism of apomorphine-induced stereotypy (mouse)[b] ED_{50} (mg/kg, po)	induction of catalepsy (mouse)[b] ED_{50} (mg/kg, po)	stereotypy[c] / climbing	catalepsy[d] / climbing
72	14.3	46.7	55.5	4	3
76	15.6	65.0	80.6	4	5
77	10.1	91.1[e]	192.4[f]	9	19
78	14.3	87.5	122.7	9	6
88	17.9	59.9	44.5	3	3
haloperidol	0.5	0.7	3.3	1	7
clozapine	22.5	78.8[g]	161.2[h]	4	7

[a] Hydrochloride salts. [b] For example protocol, see ref 19. [c] Ratio of ED_{50} for antagonism of apomorphine-induced stereotypy to ED_{50} for antagonism of apomorphine-induced climbing. [d] Ratio of ED_{50} for induction of catalepsy to ED_{50} for antagonism of apomorphine-induced climbing. [e] 95% confidence limits = 17.6−471.5 mg/kg. [f] 95% confidence limits = 98.4−375.9 mg/kg. [g] 95% confidence limits = 56.1−110.9 mg/kg. [h] 95% confidence limits = 98.7−263.2 mg/kg.

amide **77**). Further substitution on the benzamide ring was detrimental to oral activity, but the largest tolerance was in the position *ortho* to the anthranilamide nitrogen (*e.g.*, 3-fluoroanthranilamide **72**). Compounds containing remoxipride and eticlopride substitution patterns showed poor D_2/5-HT_2 selectivities; however, salicylamide **78** demonstrated interesting *in vivo* activities. The most potent derivatives were evaluated further to assess their oral activity and side-effect liabilities. Compound **77** (1192U90) was shown to be a potent, orally active derivative with efficacy-to-side effect ratios superior to those of clozapine. Like clozapine, 1192U90 more potently antagonized serotonin 5-HT_2 receptors than dopamine D_2 receptors, but unlike clozapine, it also exhibited serotonin 5-HT_{1a} agonist properties that should alleviate the anxiety that often precipitates psychotic episodes in schizophrenic patients. Additional biological evaluations indicated that 1192U90 should relieve the positive and negative symptoms of schizophrenia and have a low liability to cause EPS. Owing to its excellent pharmacological profile, 1192U90, 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride, has been selected for clinical development as an antipsychotic agent.

Experimental Section

Pharmacology. Both *in vitro* (receptor binding affinities) and *in vivo* (antagonism of apomorphine-induced mouse climbing) activities of test compounds were determined by the methods previously reported.[19]

Chemistry. General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane, toluene, pyridine, and dimethyl sulfoxide (DMSO) were obtained in Sure/Seal bottles from Aldrich Chemical Co. Triethylamine was distilled from CaH_2 prior to use. All reactions involving air- or moisture-sensitive compounds were performed under a N_2 atmosphere. Flash chromatography and flush chromatography were performed using EM Science silica gel 60 (230−400 mesh ASTM). The term flush chromatography refers to column chromatography when suction is applied to the bottom of the column to increase the flow rate of the eluent. Thin-layer chromatography (TLC) was performed with Analtech silica gel GF TLC plates (250 μm). ^{1}H NMR spectra were determined with superconducting FT NMR spectrometers operating at 200 and 300 MHz. ^{13}C NMR spectra were measured at 50.29 or 75.43 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in hertz (Hz). Elemental analyses were performed by either Atlantic Microlab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected.

4-((*tert*-Butoxycarbonyl)amino)benzoic Acid (13). 4-Aminobenzoic acid (**3**) (10.0 g, 72.9 mmol), 5% Na_2CO_3 (50 mL), and 1,4-dioxane (40 mL) were added to a 500-mL round-bottomed flask equipped with a magnetic stir bar and addition funnel. The solution was cooled in an ice−water bath, and a solution of di-*tert*-butyl dicarbonate (23.8 g, 109 mmol, 1.5 equiv) in 1,4-dioxane (40.0 mL) was added dropwise. The ice−water bath was removed, and the reaction mixture was allowed to warm to room temperature and stir for 24 h. The reaction mixture was cooled with an ice−water bath, and an additional portion of di-*tert*-butyl dicarbonate (1.0 equiv) in 1,4-dioxane (20 mL) was added dropwise. The ice−water bath was removed, and the reaction mixture was allowed to stir at room temperature for 2 days. The solvent was removed *in vacuo*, and H_2O (150 mL) was added to the resulting white solid. The pH was adjusted to *ca.*2 with 1 N HCl, and the aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a white solid. The solid was triturated with hexanes and dried to give 14.80 g (86%) of benzoic acid **13** as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.50 (s, 9), 7.58 (d, 2, J = 8.8), 7.86 (d, 2, J = 8.8), 9.76 (br s, 1), 12.67 (br s, 1).

3-((*tert*-Butoxycarbonyl)amino)benzoic Acid (14). This compound was prepared according to the method described for acid **13**, by employing 3-aminobenzoic acid (**4**) (5.0 g, 36.5 mmol), 5% Na_2CO_3 (25 mL), and di-*tert*-butyl dicarbonate (19.9 g, 91.1 mmol, 2.5 equiv). After 65 h, the reaction mixture was worked up to give 7.48 g (86%) of benzoic acid **14** as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.49 (s, 9), 7.37 (t, 1, J = 7.9), 7.54 (dd, 1, J = 1.2, 6.5), 7.63 (dd, 1, J = 0.9, 7.9), 8.15 (s, 1), 9.56 (br s, 1), 12.92 (br s, 1).

2-(2-(*tert*-Butoxycarbonyl)hydrazino)benzoic Acid (15). 2-Hydrazinobenzoic acid hydrochloride (**5**) (7.5 g, 40.0 mmol), 1,4-dioxane (40 mL), and 5% aqueous Na_2CO_3 (75 mL) were combined in a 500-mL round-bottomed flask and cooled in an ice−water bath. The flask was equipped with an addition funnel, and a solution of di-*tert*-butyl dicarbonate (9.6 g, 44.0 mmol, 1.1 eq) in 1,4-dioxane (20 mL) was slowly added. The ice−water bath was removed, and the reaction mixture was allowed to stir at room temperature for 6 h. An additional portion of di-*tert*-butyl dicarbonate (0.99 g, 4.54 mmol, 0.11 eq) was dissolved in 1,4-dioxane (10 mL) and slowly added to the reaction mixture. The reaction mixture was allowed to stir for an additional 26 h and concentrated to give a red-orange residue. Water (200 mL) was added to the residue, and the mixture was cooled in an ice−water bath. The pH was adjusted (pH = 1) by the addition of aqueous 1 N HCl, and the solution was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to give a solid. The solid was triturated with hexanes and dried in a vacuum oven to give 9.13 g (91%) of benzoic acid **15** as a tan-beige solid. ^{1}H NMR (DMSO-d_6): δ 1.43 (s, 9), 6.77

(t, 1, J = 7.5), 6.88 (d, 1, J = 8.2), 7.45 (tm, 1, J = 7.7), 7.83 (dd, 1, J = 1.5, 7.9), 8.89 (s, 1), 9.07 (br s, 1), 12.98 (br s, 1).

2-Amino-α,α,α-trifluoro-*p*-toluic Acid (21). A solution of 2-nitro-α,α,α-trifluoro-*p*-toluic acid (**6**) (5.00 g, 21.3 mmol) in absolute EtOH (100 mL) was added to a Parr hydrogenation bottle containing absolute EtOH (50 mL) and 5% palladium on charcoal (100 mg). The bottle was attached to a Parr hydrogenator, and the solution was placed under a hydrogen atmosphere at 35 psi. The reaction mixture was shaken at room temperature until consumption of hydrogen ceased (2 h). The solution was filtered through a millipore AP filter, and the filtrate was concentrated with a rotary evaporator. The residue was dried under vacuum to give 4.22 g (97%) of toluic acid **21** as a pale yellow solid. This material was used without further purification.

4-Fluoroisatoic Anhydride (39). 2-Amino-4-fluorobenzoic acid (**23**) (0.97 g, 6.25 mmol) (obtained by the reduction of 4-fluoro-2-nitrobenzoic acid (**8**) by the method described for compound **21**), anhydrous 1,4-dioxane (20 mL), and trichloromethyl chloroformate (5.0 g, 25.2 mmol, 4.0 eq) were added to a 100-mL round-bottomed flask. The reaction mixture was heated at reflux for 11 h. The reaction mixture was allowed to cool and stir at room temperature overnight. The solvent was removed with a rotary evaporator to give 1.18 g (>100% crude) of **39** as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 6.90 (dd, 1, J = 2.3, 9.6), 7.13 (dt, 1, J = 2.3, 7.6), 8.02 (dd, 1, J = 6.0, 8.8), 11.90 (br s, 1). This material was used without further purification.

6-Fluoroisatoic Anhydride (40). 2-Amino-6-fluorobenzoic acid (**24**) (3.0 g, 19.3 mmol), trichloromethyl chloroformate (15.0 g, 75.8 mmol, 3.9 eq), and anhydrous 1,4-dioxane (60 mL) were added to a 250-mL round-bottomed flask equipped with a magnetic stirring bar. The solution was placed under N_2 and heated at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and concentrated to give 3.8 g of the crude product as an off-white solid. This material was used without further purification. ^{1}H NMR (DMSO-d_6): δ 6.97 (d, 1, J = 8.2), 7.06 (dd, 1, J = 8.4, 10.7), 7.73 (m, 1), 11.90 (br s, 1).

6-Fluoroisatoic Anhydride (40) and 3-Fluoroisatoic Anhydride (41). Anhydrous $CHCl_3$ (50 mL), 3-fluorophthalic anhydride (**38**) (10.0 g, 60.2 mmol), and azidotrimethylsilane (8.0 mL, 60.2 mmol, 1.0 eq) were placed under N_2 in a flame-dried 250-mL round-bottomed flask. The reaction mixture was gently heated with a heat gun until evolution of gas was noted and then heated at reflux for 3.5 h. The solution was allowed to cool to room temperature, and 95% EtOH (10 mL) was added. The milky solution was cooled with an ice−water bath, and the resulting precipitate was filtered and dried in a vacuum oven to give 7.78 g (71%) of the title compounds as an off-white solid. Integration of the ^{1}H NMR indicated a 60:40 mixture of the 3-fluoro and 6-fluoro isomers, respectively. **41**: ^{1}H NMR (DMSO-d_6) δ 7.24 (dt, 1, J = 4.7, 8.1), 7.68 (ddd, 1, J = 1.3, 8.2, 10.7), 7.76 (dt, 1, J = 7.9, 0.9). This mixture was used without further purification.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2,6-dimethoxybenzamide Hydrochloride (47).** 3-Bromo-2,6-dimethoxybenzoic acid (**9**)[27] (1.48 g, 5.69 mmol) and anhydrous toluene (50 mL) were added to a flame-dried three-necked 100-mL round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet, addition funnel, and thermometer. Thionyl chloride (1.12 mL, 1.83 g, 15.4 mmol, 2.7 eq) was added dropwise to the reaction mixture at room temperature. The addition funnel was replaced with a reflux condenser, and the reaction mixture was heated to 65 °C. DMF (0.03 mL) was added to the reaction mixture, and the temperature was maintained at 65 °C for 2 h. The solvent was removed *in vacuo*, and the residue was taken up in $CHCl_3$ (20 mL). To this solution were added 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 0.9 eq) in $CHCl_3$ (12.0 mL) and triethylamine (1.08 mL, 0.785 g, 7.76 mmol, 1.4 eq). The reaction mixture was stirred at room temperature for 0.5 h. The solvent was removed *in vacuo*, and the orange oil was dissolved in EtOAc. The organic solution was washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give an orange oil (3.24 g). The crude material was purified by flash chromatography with EtOAc:0.1% triethylamine followed by EtOAc:0.2% triethylamine to give 1.45 g of the free base as a yellow oil. To a solution of the free base in EtOAc was added 2.72 mL of 1 N ethereal HCl (1.0 eq). The solvent was removed *in vacuo*, and the hydrochloride salt was recrystallized from EtOH to give 0.867 g (27%) of 3-bromo-2,6-dimethoxybenzamide **47** as a white solid. Mp: 220−221 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.56 (m, 2), 1.83 (m, 2), 3.24 (m, 6), 3.54 (m, 4), 3.78 (s, 6), 4.08 (br d, 2, J = 13.4), 6.85 (d, 1, J = 9.0), 7.48 (t, 1, J = 7.5), 7.59 (d, 1, J = 8.9), 7.60 (tm, 1, J = 8.1), 8.13 (t, 2, J = 8.9), 8.38 (br t, 1, J = 5.6), 10.92 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.36, 36.23, 38.01, 46.29, 50.39, 55.07, 56.12, 61.72, 106.87, 109.21, 121.16, 123.97, 124.01, 124.59, 126.92, 128.09, 132.97, 152.06, 153.45, 156.20, 162.17, 163.33. Anal. ($C_{24}H_{29}N_4O_3SBr$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2,6-dihydroxybenzamide Hydrochloride (48).** Thionyl chloride (1.46 mL, 2.4 g, 20 mmol, 3.8 eq), anhydrous DMF (0.05 mL), anhydrous toluene (15 mL), and 3-bromo-2,6-dihydroxybenzoic acid (**10**)[20] (1.2 g, 5.15 mmol) were added to a flame-dried 100-mL round-bottom flask. The solution was placed under nitrogen and heated at 60−85 °C for 1 h. The solvent was removed *in vacuo*, and anhydrous CH_2Cl_2 (15 mL) and triethylamine (1.08 mL, 0.782 g, 7.73 mmol) were added to the solid residue. To this suspension was added a solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.15 mmol) in anhydrous CH_2Cl_2 (15 mL), and the reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was transferred to a separatory funnel, CH_2Cl_2 was added, and the solution was washed with saturated $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to give 2.94 g of the crude product as a tan-beige solid. The free base was purified by flash chromatography (2×) with 93:7 CH_2Cl_2:MeOH as eluant to give 0.703 g of the free base as a yellow solid. The free base (0.703 g, 1.39 mmol) was dissolved in CH_2Cl_2 and EtOAc, and 1 N ethereal HCl (1.39 mL, 1.0 eq) was added. The hydrochloride salt was filtered, washed with ether, and dried in a vacuum oven to give 0.454 g (16%) of 3-bromo-2,6-dihydroxybenzamide **48** as an off-white solid. Mp: 228−230 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.62 (m, 2), 1.77 (m, 2), 3.00−3.70 (m, 10), 4.05 (m, 2), 6.49 (d, 1, J = 8.8), 7.48 (tm, 1, J = 7.2), 7.48 (d, 1, J = 8.8), 7.60 (t, 1, J = 7.6), 8.13 (t, 2, J = 8.8), 9.09 (br s, 1), 10.50 (br s, 1), 11.85 (br s, 1), 14.81 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.71, 26.05, 38.32, 46.47, 50.58, 55.16, 99.68, 103.61, 107.57, 121.25, 124.05, 124.68, 127.00, 128.18, 135.99, 152.15, 157.05, 159.25, 162.26, 169.57. Anal. ($C_{22}H_{25}BrN_4O_3S$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-2,6-dimethoxybenzamide Hydrochloride (49).** Toluene (100 mL) and 3-chloro-5-ethyl-2,6-dimethoxybenzoic acid (**11**)[21] (4.32 g, 17.6 mmol) were added to an oven-dried 300-mL round-bottomed flask. The solution was placed under N_2, and thionyl chloride (4.13 mL, 5.67 g, 47.6 mmol, 2.7 equiv) was added. The light yellow reaction mixture was heated to 75 °C, and anhydrous DMF (0.25 mL) was added. The solution was heated at 65−75 °C for 1.25 h. The solvent was removed with a rotary evaporator to give acid chloride **27** as an orange residue. This crude acid chloride was dissolved in anhydrous $CHCl_3$ (50 mL) and placed under N_2. A solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (5.63 g, 19.4 mmol, 1.1 equiv) in anhydrous $CHCl_3$ (20 mL) was added to the acid chloride solution. Dry triethylamine (2.94 mL, 2.14 g, 2.10 mmol, 1.2 equiv) was added. The reaction mixture was allowed to stir at room temperature for 0.75 h, and the solvent was removed with a rotary evaporator. The resulting viscous orange residue was dissolved in CH_2Cl_2 and washed with saturated aqueous K_2CO_3. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give 10.03 g of an orange viscous oil. The crude material was adsorbed on silica gel and purified by flash chromatography on silica gel with EtOAc:0.1% triethylamine as eluant to give 4.78 g of a pale yellow oil. The hydrochloride salt was prepared by adding HCl (9.24 mL of a 1 N solution in ether, 1.0 equiv) to a solution of the free base in EtOH. The salt was recrystal-

lized from EtOH/ether and dried in a vacuum oven to give 2.96 g (30%) of 3-chloro-5-ethyl-2,6-dimethoxybenzamide **49** as light tan powder. Mp: 198.5−200 °C. ^{1}H NMR (DMSO-d_6): δ 1.16 (t, 3, J = 7.5), 1.60 (m, 2), 1.83 (br s, 2), 2.58 (q, 2, J = 7.5), 3.20−3.63 (m, 10), 3.74 (s, 3), 3.78 (s, 3), 4.10 (br d, 2, J = 12.1), 7.38 (s, 1), 7.49 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 8.14 (t, 2, J = 7.0), 8.50 (t, 1, J = 5.3), 10.66 (s, 1). ^{13}C NMR (DMSO-d_6): δ 14.76, 20.73, 21.80, 26.46, 46.57, 50.67, 55.39, 61.89, 62.27, 121.49, 121.76, 124.30, 124.95, 127.28, 128.45, 129.16, 130.17, 134.64, 150.88, 152.48, 153.96, 162.56, 164.26. Anal. ($C_{26}H_{33}N_4O_3SCl$·HCl) C, H, N.

2-Azido-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide Hydrochloride (50). 2-Azidobenzoic acid (**12**)[22] (0.8 g, 5.15 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.16 mmol, 1.0 eq), 1-hydroxybenzotriazole hydrate (0.768 g, 5.68 mmol, 1.1 equiv), and anhydrous DMF (25 mL) were added to a 250-mL round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and nitrogen inlet. The reaction mixture was cooled in an ice−water bath, and a solution of 1,3-dicyclohexylcarbodiimide (1.17 g, 5.67 mmol, 1.1 equiv) in DMF (30 mL) was added dropwise. The ice−water bath was removed, and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was filtered, and the filtrate was concentrated. The crude product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography with CH_2Cl_2:MeOH (100−93%:0−7%) as eluant to give 1.74 g of the free base as an orange oil. The free base (1.52 g, 3.49 mmol) was dissolved in CH_2Cl_2, and 1 N ethereal HCl (1.0 equiv) was added. The solvent was removed *in vacuo* to give an amorphous solid. The solid was dissolved in MeOH, and the solution was filtered. The filtrate was slowly added to EtOAc. The precipitated solid was filtered, rinsed with diethyl ether, and dried in a vacuum oven to give 1.24 g (51%) of 2-azidobenzamide **50** as a pale beige solid. Mp: 163.5−164 °C. ^{1}H NMR (DMSO-d_6): δ 1.56 (quin, J = 7.0), 1.81 (m, 2), 3.24 (m, 6), 3.46 (br d, 2, J = 12.3), 3.56 (br d, 2, J = 11.8), 4.05 (br d, 2, J = 13.4), 7.22 (tm, 1, J = 7.5), 7.33 (dd, 1, J = 1.2, 8.5), 7.48 (m, 3), 7.58 (ddd, 1, J = 1.1, 6.9, 8.0), 8.10 (t, 2, J = 8.1), 8.37 (br t, 1, J = 5.6), 10.97 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.85, 26.55, 38.70, 46.68, 50.74, 55.44, 119.90, 121.53, 124.34, 124.95, 125.20, 127.31, 128.45, 129.09, 129.89, 131.54, 136.79, 152.45, 162.58, 165.91. IR (KBr): 2126 cm^{-1}. Anal. ($C_{22}H_{25}N_7OS$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide Hydrochloride (52).** The free base of this compound was prepared according to the method described for compound **82**. Acylation of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 1.0 equiv) with benzoyl chloride (**30**) (0.6 mL, 0.727 g, 5.17 mmol) over a 1-h period gave 1.49 g of the free base, which was purified by flash chromatography with EtOAc:0.1% triethylamine. To a solution of the free base in EtOAc was added HCl (3.8 mL of a 1 N solution in ether, 1.0 equiv). The hydrochloride salt was recrystallized from EtOH to give 1.04 g (47%) of benzamide **52** as a pale beige solid. Mp: 200−201.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.80 (m, 2), 3.27 (m, 6), 3.47 (br t, 2, J = 12.6), 3.59 (br d, 2, J = 11.7), 4.08 (br d, 2, J = 13.4), 7.50 (m, 4), 7.60 (t, 1, J = 7.6), 7.87 (m, 2), 8.13 (t, 2, J = 8.4), 8.58 (br t, 1, J = 5.5), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.59, 26.25, 38.36, 46.32, 50.41, 55.09, 121.14, 123.95, 124.56, 126.90, 127.12, 128.07, 128.16, 131.01, 134.47, 152.05, 162.16, 166.15. Anal. ($C_{22}H_{26}N_4OS$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-chlorobenzamide Hydrochloride Hydrate (53).** 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.5 equiv), and CH_2Cl_2 (10.0 mL) were added to a flame-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet, and addition funnel. The reaction mixture was cooled in an ice−water bath, and a solution of 4-chlorobenzoyl chloride (**31**) (0.61 g, 3.45 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) was added dropwise. The reaction mixture was allowed to stir for 0.5 h and transferred to a separatory funnel with the aid of EtOAc. The organic solution was washed with saturated potassium carbonate, dried over $MgSO_4$, filtered, and concentrated to give a pale yellow solid (1.4 g). The crude reaction mixture was purified by flash chromatography with EtOAc:0.1% triethylamine as eluant to give 0.99 g of the free base as a white solid. The free base was dissolved in EtOAc and CH_2Cl_2, and 2.31 mL of 1 N ethereal HCl (1.0 equiv) was added. The solvent was removed *in vacuo*, and the hydrochloride salt was recrystallized from EtOH/H_2O to give 0.915 g (56%) of 4-chlorobenzamide **53** as a white solid. Mp: 209−210 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.60 (m, 2), 1.79 (m, 2), 3.15−3.37 (m, 5), 3.45 (br t, 3, J = 12.7), 3.59 (br d, 2, J = 12.0), 4.08 (br d, 2, J = 12.9), 7.48 (ddd, 1, J = 1.0, 7.1, 8.1), 7.55 (dm, 2, J = 8.6), 7.60 (ddd, 1, J = 1.2, 7.0, 8.2), 7.90 (dm, 2, J = 8.7), 8.13 (t, 2, J = 8.2), 8.68 (br t, 1, J = 5.5), 10.59 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.58, 26.17, 38.44, 46.32, 50.41, 55.08, 121.13, 123.95, 124.56, 126.91, 128.07, 128.25, 129.10, 133.18, 135.84, 152.05, 162.16, 165.09. Anal. ($C_{22}H_{25}N_4OSCl$·HCl·0.5H_2O) C, H, N, H_2O.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3,4-dichlorobenzamide Hydrochloride (54).** This compound was prepared according to the method described for benzamide **53**, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.5 eq), and 3,4-dichlorobenzoyl chloride (**32**) (0.723 g, 3.45 mmol, 1.0 eq). The crude reaction mixture was purified by flash chromatography with EtOAc: 0.1% triethylamine as eluant to give the free base (1.52 g) as a white solid. The hydrochloride salt was prepared, recrystallized from EtOH/H_2O, and dried in a vacuum oven to given 0.88 g (51%) of 3,4-dichlorobenzamide **54** as a pale beige solid. Mp: 208−210 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.82 (m, 2), 3.27 (m, 6), 3.52 (m, 4), 4.07 (br d, 2, J = 13.4), 7.47 (t, 1, J = 7.6), 7.60 (t, 1, J = 7.5), 7.76 (d, 1, J = 8.5), 7.88 (dd, 1, J = 2.0, 8.4), 8.12 (t, 2, J = 8.2), 8.14 (d, 1, J = 2.0), 8.86 (t, 1, J = 5.5), 11.10 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.58, 26.07, 38.62, 46.33, 50.44, 55.08, 121.14, 123.95, 124.57, 126.91, 127.52, 128.07, 129.13, 130.59, 131.16, 133.85, 134.75, 152.07, 162.17, 163.88. Anal. ($C_{22}H_{24}N_4OSCl_2$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-methoxybenzamide Hydrochloride (55).** This compound was prepared according to the method described for benzamide **53**, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.5 equiv), and *p*-anisolyl chloride (**33**) (0.589 g, 3.45 mmol, 1.0 equiv). The crude reaction mixture was purified by flash chromatography with 93:7 CH_2Cl_2:MeOH as eluant to give the free base as a pale beige solid (0.73 g). The hydrochloride salt was prepared, recrystallized from EtOH, and dried in a vacuum oven to give 0.287 g (18%) of 4-methoxybenzamide **55** as a tan solid. Mp: 171−173 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.78 (m, 2), 3.26 (m, 6), 3.49 (br d, 2, J = 12.1), 3.58 (br d, 2, J = 13.8), 3.81 (s, 3), 4.07 (br d, 2, J = 13.4), 7.00 (dm, 2, J = 8.9), 7.48 (ddd, 1, J = 1.2, 7.0, 8.1), 7.60 (ddd, 1, J = 1.0, 7.0, 8.1), 7.86 (dm, 2, J = 8.9), 8.13 (t, 2, J = 8.3), 8.45 (t, 1, J = 5.6), 10.81 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.63, 26.35, 38.29, 46.35, 50.43, 55.13, 55.27, 113.35, 121.15, 123.96, 124.58, 126.69, 126.92, 128.08, 128.94, 152.07, 161.39, 162.17, 165.64. Anal. ($C_{23}H_{28}N_4O_2S$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-(trifluoromethyl)benzamide Hydrochloride (56).** This compound was prepared according to the method described for benzamide **53**, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.5 equiv), and 4-(trifluoromethyl)benzoyl chloride (**34**) (0.513 mL, 0.720 g, 3.45 mmol, 1.0 equiv). After the 4-(trifluoromethyl)benzoyl chloride was added, the ice−water bath was removed and the reaction mixture was stirred for 1.5 h. The crude reaction mixture was purified by flash chromatography with 1:1 EtOAc:hexanes with 0.1% triethylamine as eluant followed by EtOAc:0.1% triethylamine to give 0.57 g of the free base as a solid. The hydrochloride salt was prepared and recrystallized from EtOH to give 0.26 g (15%) of 4-(trifluoromethyl)benzamide **56** as a

tan solid. Mp: 205−207 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.62 (m, 2), 1.83 (m, 2), 3.15−3.40 (m, 6), 3.50 (br t, 2, J = 13.0), 3.59 (br d, 2, J = 11.6), 4.08 (br d, 2, J = 13.3), 7.48 (ddd, 1, J = 1.0, 7.1, 8.1), 7.60 (ddd, 1, J = 1.0, 6.9, 8.1), 8.08 (d, 2, J = 8.8), 8.11 (m, 4), 8.87 (br t, 1, J = 5.5), 10.95 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.63, 26.15, 38.50, 46.37, 50.47, 55.12, 121.18, 122.13, 123.99, 124.61, 125.23, 126.95, 128.11, 130.79, 138.25, 152.10, 162.20, 165.04. Anal. ($C_{23}H_{25}N_4OSF_3$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-*tert*-butylbenzamide Hydrochloride (57).** This compound was prepared according to the method described for benzamide **53**, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.0 g, 3.45 mmol), triethylamine (0.721 mL, 0.524 g, 5.18 mmol, 1.0 equiv), and 4-*tert*-butylbenzoyl chloride (**35**) (0.674 mL, 0.679 g, 3.45 mmol, 1.0 equiv). The hydrochloride salt was prepared from the free base (0.560 g) and recrystallized from EtOH to give 0.251 g (15%) of 4-*tert*-butylbenzamide **57** as a tan solid. Mp: 220.5−222 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.31 (s, 9), 1.60 (m, 2), 1.82 (m, 2), 3.25 (m, 6), 3.55 (m, 4), 4.08 (br d, 2, J = 13.3), 7.49 (m, 3), 7.62 (t, 1, J = 7.4), 7.83 (d, 2, J = 8.4), 8.14 (m, 2), 8.55 (t, 1, J = 5.7), 11.06 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.82, 26.55, 31.15, 34.77, 38.53, 46.63, 50.71, 55.39, 121.51, 124.32, 124.93, 125.28, 127.28, 127.35, 128.45, 132.11, 152.45, 154.15, 162.57, 166.47. Anal. ($C_{26}H_{34}N_4OS$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-(phenylazo)benzamide Hydrochloride (58).** This compound was prepared according to the method described for benzamide **53**, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.24 g, 4.27 mmol), triethylamine (0.893 mL, 0.648 g, 6.41 mmol, 1.5 equiv), and *p*-(phenylazo)-benzoyl chloride (**36**) (1.05 g, 4.27 mmol, 1.0 equiv). The reaction mixture was allowed to stir for 1 h following the addition of *p*-(phenylazo)benzoyl chloride. The free base was purified by flash chromatography with 3:1 EtOAc:hexanes with 0.1% triethylamine followed by EtOAc:0.1% triethylamine and, finally, EtOAc:0.2% triethylamine as eluant to give 1.42 g of the compound as an orange solid. The free base was recrystallized from EtOAc to give 0.781 g of the pure compound as an orange solid. The hydrochloride salt was prepared and recrystallized from EtOH/H_2O to give 0.589 g (26%) of 4-(phenylazo)benzamide **58** as an orange solid. Mp: 225−227 °C. ^{1}H NMR (DMSO-d_6): δ 1.67 (m, 2), 1.82 (m, 2), 3.36 (m, 8), 3.63 (br d, 2, J = 10.4), 4.11 (br d, 2, J = 11.9), 7.49 (tm, 1, J = 7.6), 7.64 (m, 4), 7.98 (m, 4), 8.14 (m, 4), 8.82 (br t, 1, J = 5.6), 10.50 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.65, 26.22, 38.56, 46.36, 50.45, 55.12, 119.43, 119.91, 121.16, 122.30, 122.68, 123.97, 124.58, 126.91, 127.45, 127.95, 128.09, 128.50, 128.84, 129.52, 131.98, 132.61, 136.64, 151.82, 152.07, 153.15, 153.46, 155.71, 162.17, 165.18, 165.39. Anal. ($C_{28}H_{30}N_6OS$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-nitrobenzamide Hydrochloride (59).** This compound was prepared according to the method for compound **53**, by employing 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (0.99 g, 3.4 mmol), triethylamine (0.72 mL, 0.52 g, 5.1 mmol, 1.5 equiv), and 2-nitrobenzoyl chloride (**37**) (0.70 g, 3.4 mmol, 1.0 equiv). The crude reaction mixture was purified by flash chromatography with EtOAc:0.1% triethylamine as eluant to give 0.94 g of the free base as a yellow solid. the hydrochloride salt was prepared, recrystallized from EtOH/ether, and dried in a vacuum oven to give 0.66 g (41%) of 2-nitrobenzamide **59** as an off-white powder. Mp: 214−215 °C. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.85 (m, 2), 3.28 (m, 6), 3.56 (m, 4), 4.09 (br d, 2, J = 13.5), 7.48 (dd, 1, J = 7.2, 7.8), 7.72 (m, 4), 8.06 (d, 1, J = 8.0), 8.15 (t, 2, J = 7.0), 8.83 (br t, J = 5.5), 11.29 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.44, 26.95, 39.32, 47.30, 51.39, 56.06, 122.18, 124.86, 124.99, 125.59, 127.94, 129.09, 130.07, 131.63, 133.57, 134.55, 148.01, 153.09, 163.20, 166.42. Anal. ($C_{22}H_{25}N_5O_3S$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-((*tert*-butoxycarbonyl)amino)benzamide Hydrochloride (60).** This compound was prepared according to the method described for benzamide **63**, by employing 4-((*tert*-butoxycarbonyl)amino)benzoic acid (**13**) (2.05 g, 8.65 mmol), triethylamine (1.45 mL, 1.05 g, 10.4 mmol, 1.2 equiv), isobutyl chloroformate (1.12 mL, 1.18 g, 8.65 mmol, 1.0 equiv), and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.51 g, 8.65 mmol, 1.0 equiv). The crude reaction mixture was purified by flash chromatography with EtOAc:0.1% triethylamine as eluant to give 0.78 g of the free base as a white solid. Impure fractions were combined and purified by flash chromatography with 9:1 CH_2Cl_2:MeOH as eluant to give 0.40 g of the free base as a white solid. The free base obtained from each column was combined and dissolved in EtOH and $CHCl_3$. To a solution of the free base was added 1 N ethereal HCl (2.41 mL, 1.0 equiv). The solvent was removed, and the hydrochloride salt was recrystallized from EtOH to give 0.644 g (14%) of 4-((*tert*-butoxycarbonyl)amino)benzamide **60** as a beige solid. Mp: 205−208 °C effervesces. ^{1}H NMR (DMSO-d_6): δ 1.49 (s, 9), 1.60 (m, 2), 1.80 (m, 2), 3.10−3.54 (m, 8), 3.59 (m, 2), 4.08 (br d, 2, J = 12.5), 7.55 (m, 4), 7.80 (d, 2, J = 8.8), 8.14 (m, 2), 8.45 (br t, 1, J = 5.4), 9.64 (s, 1), 10.80 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.64, 26.34, 28.01, 38.28, 46.36, 50.33, 55.12, 79.39, 117.00, 121.15, 123.96, 124.58, 126.92, 127.79, 127.96, 128.08, 142.11, 152.06, 152.54, 162.17, 165.70. Anal. ($C_{27}H_{35}N_5O_3S$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-((*tert*-butoxycarbonyl)amino)benzamide Hydrochloride Hydrate (61).** This compound was prepared according to the method described for benzamide **63**, by employing 3-((*tert*-butoxycarbonyl)amino)benzoic acid (**14**) (2.45 g, 10.3 mmol), triethylamine (1.72 mL, 1.25 g, 12.4 mmol, 1.2 equiv), isobutyl chloroformate (1.34 mL, 1.41 g, 10.3 mmol, 1.0 equiv), and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (3.0 g, 10.3 mmol, 1.0 equiv). After 20 h, the reaction mixture was transferred to a separatory funnel with the aid of CH_2Cl_2. The solution was washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give the crude free base. The crude product was purified by flash chromatography with 95:5 CH_2Cl_2:MeOH as eluant to give 2.82 g of the free base as a white solid. To a solution of the free base (1.0 g, 1.96 mmol) in $CHCl_3$ was added 1.96 mL of 1 N ethereal HCl (1.0 equiv). The hydrochloride salt was recrystallized from EtOH/ether to give 0.46 g (23%) of 3-((*tert*-butoxycarbonyl)amino)benzamide **61** as a white solid. Mp: 139−144 °C effervesces. ^{1}H NMR (DMSO-d_6): δ 1.48 (s, 9), 1.59 (m, 2), 1.80 (m, 2), 3.16−3.54 (m, 8), 3.59 (br d, 2, J = 11.8), 4.08 (br d, 2, J = 13.1), 7.32 (t, 1, J = 7.9), 7.48 (m, 3), 7.60 (ddd, 1, J = 1.1, 6.9, 8.1), 8.00 (s, 1), 8.13 (t, 2, J = 8.1), 8.50 (br t, 1, J = 5.6), 9.49 (s, 1), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.84, 26.48, 29.29, 38.66, 46.62, 50.71, 55.41, 79.43, 117.68, 120.82, 121.04, 121.50, 124.31, 124.93, 127.27, 128.44, 128.72, 135.72, 139.92, 152.45, 153.12, 162.56, 166.82. Anal. ($C_{27}H_{35}N_5O_3S$·HCl·0.75H_2O) C, H, N, H_2O.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-(2-(*tert*-butoxycarbonyl)hydrazino)benzamide (62).** 2-(2-(*tert*-Butoxycarbonyl)hydrazino)benzoic acid (**15**) (2.57 g, 10.2 mmol), anhydrous THF (30 mL), and anhydrous triethylamine (1.70 mL, 1.23 g, 12.2 mmol, 1.2 equiv) were combined in a flame-dried 100-mL round-bottom flask. The orange solution was stirred under a nitrogen atmosphere and cooled between −20 and −35 °C with a dry ice/2-propanol bath. Isobutyl chloroformate (1.32 mL, 1.39 g, 1.0 equiv) was added, and the mixture was allowed to stir for 5 min. A cold (−20 to −35 °C) solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.97 g, 10.2 mmol, 1.0 equiv) in anhydrous THF (30 mL) was slowly added. The reaction mixture was allowed to stir between −15 and −30 °C for 0.75 h. The cold bath was removed, and the reaction mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was transferred to a separatory funnel, CH_2Cl_2 was added, and the solution was washed with saturated $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 5.89 g of an orange oil. The crude product was purified by column chromatography with 19:1 CH_2Cl_2:MeOH as eluant to give 3.01 g (56%) of (2-(*tert*-butoxycarbonyl)hydrazino)benzamide **62** as a pale beige glass. ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9), 1.68 (br t, 4, J = 3.0), 2.49 (br t, 2, J = 6.8), 2.67 (br t, 4, J = 4.8), 3.45 (br q, 2, J = 6.0), 3.55 (br t, 4,

J = 4.8), 6.32 (br s, 1), 6.61 (m, 1), 6.78 (tm, 1, J = 7.5), 7.01 (d, 1, J = 8.2), 7.35 (m, 3), 7.47 (tm, 1, J = 7.5), 7.81 (d, 1, J = 8.0), 7.90 (d, 1, J = 8.0), 8.76 (br s, 1).

4-Acetamido-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide Hydrochloride (63). 4-Acetamidobenzoic acid (**16**) (0.742 g, 414 mmol), triethylamine (0.693 mL, 0.503 g, 4.97 mmol, 1.2 equiv), and anhydrous THF (20 mL) were added to a flame-dried 100-mL three-necked round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet, thermometer, and rubber septum. The reaction mixture was cooled to −15 °C with a dry ice/2-propanol bath. To the reaction mixture was added isobutyl chloroformate (0.537 mL, 0.565 g, 4.14 mmol, 1.0 equiv). After 5 min, a solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.20 g, 4.14 mmol, 1.0 equiv) in anhydrous THF (10.0 mL) was added dropwise. The reaction mixture was stirred at −15 °C for 1 h and then allowed to warm to room temperature. After 18 h, the reaction mixture was transferred to a separatory funnel with the aid of CH_2Cl_2 and washed with saturated K_2CO_3. The organic layer was filtered, dried with $MgSO_4$, filtered, and concentrated to give a yellow oil (1.70 g). The crude product was purified by flash chromatography with 9:1 CH_2Cl_2:MeOH to give 0.74 g of the free base as a white foam. To a solution of the free base in EtOAc and CH_2Cl_2 was added 1.57 mL of 1 N ethereal HCl (1.0 equiv). The solvent was removed *in vacuo*, and the salt was recrystallized from EtOH/H_2O to give 0.474 g (23%) of 4-acetamidobenzamide **63** as a pale cream solid. Mp: >250 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 2.07 (s, 3), 3.25 (m, 6), 3.46 (br t, 2, J = 12.9), 3.59 (br d, 2, J = 11.4), 4.08 (br d, 2, J = 13.4), 7.48 (t, 1, J = 7.5), 7.60 (t, 1, J = 7.6), 7.66 (d, 2, J = 8.7), 7.82 (d, 2, J = 8.6), 8.13 (t, 2, J = 8.3), 8.46 (br t, 1, J = 5.2), 10.23 (s, 1), 10.68 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.67, 24.09, 26.37, 38.34, 46.40, 50.49, 55.18, 118.01, 121.19, 124.00, 124.61, 126.95, 127.98, 128.12, 128.75, 141.84, 152.11, 162.20, 165.73, 168.66. Anal. ($C_{24}H_{29}N_5O_2S$·HCl) C, H, N.

Anthranilamides 64−67 and 69. These compounds were prepared from the corresponding substituted anthranilinic acid precursors by the method described for compound **68**. The anthranilic acids employed were obtained from commercial suppliers or prepared by known methods as indicated. The analytical data for these 2-aminobenzamides are shown below.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-methylbenzamide Hydrochloride (64). Starting material: 2-amino-3-methylbenzoic acid (**17**). Yield: 0.806 g (54%). Mp: 208−210 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.78 (m, 2), 2.08 (s, 3), 3.31 (m, 8), 3.59 (m, 2), 4.08 (br d, 2, J = 12.1), 6.21 (br s, 2), 6.48 (t, 1, J = 7.6), 7.07 (d, 1, J = 7.1), 7.39 (d, 1, J = 7.8), 7.47 (t, 1, J = 7.5), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 8.3), 8.30 (br t, 1, J = 5.2), 10.58 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 18.57, 21.73, 27.27, 39.08, 47.44, 51.52, 56.24, 115.39, 115.75, 122.16, 123.95, 124.97, 125.61, 126.88, 127.92, 129.11, 133.36, 148.47, 153.08, 163.18, 170.34. MS (CI/CH_4, 50 mA/s): M + 1, base (424). Anal. ($C_{23}H_{29}N_5OS$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-6-chlorobenzamide Hydrochloride (65). Starting material: 2-amino-6-chlorobenzoic acid (**18**). Yield: 0.75 g (24%). Mp: 211−213 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.59 (m, 2), 1.82 (m, 2), 3.15−3.61 (m, 10), 4.08 (br d, 2, J = 13.5), 5.23 (br s, 2), 6.61 (d, 1, J = 7.8), 6.66 (d, 1, J = 8.2), 7.05 (t, 1, J = 8.0), 7.49 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 8.14 (t, 2, J = 7.2), 8.47 (br t, 1, J = 5.3), 10.70 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.70, 27.06, 39.18, 47.40, 51.48, 56.21, 114.59, 117.02, 122.16, 122.66, 124.98, 125.61, 127.93, 129.11, 130.98, 131.18, 148.13, 153.08, 163.18, 166.48. MS (CI/CH_4, 50 mA/s): M + 1, base (444). Anal. ($C_{22}H_{26}N_5SOCl$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-5-fluorobenzamide Hydrochloride (66). Starting material: 2-amino-5-fluorobenzoic acid (**19**). Yield: 0.65 g (22%). Mp: 219−221 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.80 (m, 2), 3.29 (m, 6), 3.45 (m, 2), 3.59 (br d, 2, J = 10.9), 4.08 (br d, 2, J = 12.6), 6.30 (br s, 2), 6.71 (dd, 1, J = 8.9, 5.1), 7.05 (dt, 1, J = 2.7, 9.9), 7.37 (dd, 1, J = 2.7, 10.3), 7.47 (t, 1, J = 7.5), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 8.3), 8.37 (br t, 1, J = 5.3), 10.65 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 21.72, 27.17, 39.12, 47.42, 51.51, 56.21, 114.36, 114.67, 115.39, 115.46, 118.45, 118.54, 119.82, 120.12, 122.16, 124.97, 125.61, 127.92, 129.11, 147.27, 152.10, 153.07, 155.15, 163.18, 168.80, 168.84. MS (CI/CH_4, 50 mA/s): M + 1, base (428). Anal. ($C_{22}H_{26}N_5FOS$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-6-methylbenzamide Hydrochloride (67). Starting material: 2-amino-6-methylbenzoic acid (**20**). Yield: 1.10 g (21%). Mp: 194−196 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.80 (m, 2), 2.21 (s, 3), 3.32 (m, 6), 3.55 (m, 4), 4.10 (m, 2), 4.93 (br s, 1), 6.44 (d, 1, J = 7.4), 6.55 (d, 1, J = 8.0), 6.96 (t, 1, J = 7.7), 7.50 (t, 1, J = 7.5), 7.67 (t, 1, J = 7.5), 8.15 (t, 2, J = 7.1), 8.30 (br t, 1, J = 5.3), 10.80 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.68, 21.73, 27.27, 39.02, 47.37, 51.44, 56.17, 113.70, 118.82, 122.18, 124.18, 124.99, 125.61, 127.93, 129.11, 129.76, 135.30, 146.32, 153.08, 163.20, 169.29. MS (CI/CH_4, 50 mA/s): M + 1, base (424). Anal. ($C_{23}H_{29}N_5SO$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4-(trifluoromethyl)benzamide Hydrochloride (68). Anhydrous pyridine (20 mL), 2-amino-α,α,α-trifluoro-*p*-toluic acid (**21**) (1.33 g, 6.5 mmol), and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.00 g, 6.5 mmol, 1.0 equiv) were placed in a 100-mL round-bottom flask. The solution was placed under N_2, silicon tetrachloride (1.48 mL, 2.19 g, 13.0 mmol, 2 equiv) was slowly added with stirring, and the solution was heated at 145 °C for 18 h. The reaction mixture was allowed to cool to room temperature, poured onto crushed ice, and concentrated *in vacuo*. Distilled H_2O (200 mL) was added to the residue, and the solution was concentrated to dryness. Toluene (200 mL) was added to the resulting brown solid, and the solvent was removed with a rotary evaporator. This procedure was repeated with two additional portions of toluene (200 mL). Distilled H_2O (200 mL) was added to the residue, and the solution was made basic (pH = 11) by the addition of 1 N Na_2CO_3. The aqueous solution was extracted with EtOAc (3 × 200 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Toluene (200 mL) was added to the residue, and the solvent was removed with a rotary evaporator. This procedure was repeated with two additional portions of toluene (200 mL). The crude material was placed under high vacuum overnight and purified by flash chromatography on silica gel with a gradient eluant of EtOAc:MeOH (100−98%:0−2%) to give 1.45 g of the free amine. The product was dissolved in EtOH, and HCl (3.04 mL of a 1 N solution in ether, 1 equiv) was added. The hydrochloride salt was recrystallized from EtOH/H_2O to give 0.512 g (15%) of 2-amino-4-(trifluoromethyl)benzamide **68** as white crystals. Mp: 205−207 °C. ^{1}H NMR (DMSO-d_6): δ 1.60 (m, 2), 1.80 (m, 2), 3.28 (m, 6), 3.56 (m, 4), 4.09 (d, 2, J = 13.8), 6.74 (s, 2), 6.81 (d, 1, J = 8.3), 7.07 (s, 1), 7.49 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 7.71 (d, 1, J = 8.3), 8.14 (m, 2), 8.57 (br t, 1, J = 5.4), 10.94 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.75, 26.22, 38.21, 46.45, 50.55, 55.22, 110.09, 110.13, 110.18, 110.23, 112.29, 112.35, 112.40, 112.45, 117.88, 121.24, 122.23, 124.04, 124.66, 125.84, 127.00, 128.17, 129.34, 131.38, 131.79, 149.66, 152.16, 162.24, 167.88. MS (CI/CH_4, 50 mA/s): M + 1, base (478). Anal. ($C_{23}H_{26}N_5OSF_3$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-5-methoxybenzamide Hydrochloride (69). Starting material: 2-amino-5-methoxybenzoic acid (**22**) (obtained by the reduction of 2-nitro-5-methoxybenzoic acid (**7**) according to the method described for compound **21**). Yield: 0.313 g (10%). Mp: 150 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.60 (m, 2), 1.79 (m, 2), 3.37 (m, 12), 3.71 (s, 3), 3.88 (m, 2), 6.67 (d, 1, J = 8.8), 6.86 (dd, 1, J = 2.7, 8.8), 7.10 (d, 1, J = 2.7), 7.48 (t, 1, J = 7.5), 7.62 (t, 1, J = 7.5), 8.12 (d, 1, J = 7.5), 8.15 (d, 1, J = 7.5), 8.37 (br t, 1, J = 4.7). ^{13}C NMR (DMSO-d_6): δ 21.84, 27.33, 39.08, 47.54, 51.60, 56.29, 56.60, 113.18, 116.18, 118.66, 120.20, 122.16, 124.97, 125.59, 127.94, 129.09, 144.58, 150.34, 153.08, 163.22, 169.58. MS (CI/CH_4, 50 mA/s): M + 1, base (440). Anal. ($C_{23}H_{29}N_5O_2S$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4-fluorobenzamide Hydrochloride (70). This compound was prepared by the method described for compound

71. From 4-fluoroisatoic anhydride (**39**) (1.18 g, 6.51 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.0 g, 6.51 mmol, 1.0 equiv) was obtained 1.31 g (43%) of **70** as a pale yellow solid. Mp: 234−236 °C. ^{1}H NMR (DMSO-d_6): δ 1.53 (m, 2), 1.78 (m, 2), 3.26 (m, 6), 3.53 (m, 4), 4.07 (d, 2, J = 13.4), 6.31 (dt, 1, J = 2.5, 8.5), 6.45 (dd, 1, J = 2.5, 7.2), 6.75 (br s, 2), 7.47 (t, 1, J = 7.5), 7.60 (m, 2), 8.12 (t, 2, J = 8.3), 8.32 (br t, 1, J = 5.3), 10.90 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.66, 27.25, 39.02, 47.37, 51.47, 56.17, 102.14, 102.33, 102.45, 102.63, 112.35, 112.37, 122.18, 124.97, 125.59, 127.93, 129.11, 131.51, 131.66, 152.97, 153.09, 153.13, 163.17, 163.66, 166.92, 169.10. MS (CI/CH_4, 50 mA/s): M + 1, base (428). Anal. ($C_{22}H_{26}N_5OFS$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-6-fluorobenzamide Hydrochloride (71). 6-Fluoroisatoic anhydride (**40**) (1.5 g, 8.28 mmol) and anhydrous THF (40 mL) were added to a flame-dried 300-mL round-bottom flask. The reaction mixture was placed under N_2, and a solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.4 g, 8.28 mmol, 1.0 equiv) in anhydrous THF (25 mL) was added. The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated, and the crude free base was purified by column chromatography with 19:1 CH_2Cl_2:MeOH as eluant to give 2.79 g of the free base as a yellow oil. The free base was dissolved in EtOAc, and 1 N ethereal HCl (6.53 mL, 1.0 equiv) was added. The hydrochloride salt was recrystallized from EtOH/H_2O to give 2.0 g (52%) of 2-amino-6-fluorobenzamide **71** as a beige solid. Mp: 218−220 °C. ^{1}H NMR (DMSO-d_6): δ 1.57 (m, 2), 1.80 (m, 2), 3.10−3.75 (m, 10), 4.10 (br d, 2, J = 13.1), 5.89 (br s, 2), 6.34 (dd, 1, J = 8.0, 10.5), 6.53 (d, 1, J = 8.2), 7.09 (ddd, 1, J = 6.8, 8.0, 8.2), 7.49 (t, 1, J = 7.6), 7.62 (t, 1, J = 7.5), 8.15 (t, 2, J = 7.2), 8.28 (m, 1), 10.55 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.75, 26.38, 38.39, 46.57, 50.66, 55.38, 101.81, 102.27, 107.65, 108.01, 111.63, 111.68, 121.49, 124.32, 124.93, 127.29, 128.44, 131.20, 131.42, 149.90, 150.03, 152.46, 158.21, 162.58, 163.05, 164.66. Anal. ($C_{22}H_{26}FN_5OS$·HCl) C, H, N.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-fluorobenzamide Hydrochloride (72). THF (50 mL), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.55 g, 8.80 mmol) and a 60:40 mixture of 3-fluoro- and 6-fluoroisatoic anhydride (1.59 g, 8.80 mmol, 1.0 equiv) were placed in a 100-mL round-bottomed flask. The reaction mixture was allowed to stir at room temperature for 10 min, and the solvent was removed with a rotary evaporator. The resulting viscous oil was purified by flash chromatography (4×) on silica gel with 2:1 EtOAc:hexanes followed by EtOAc as eluant to give 0.88 g of the title compound as its free base. This material was dissolved in EtOAc, and HCl (1.89 mL of a 1 N solution in ether, 1.0 equiv) was added. The hydrochloride salt was recrystallized twice from EtOH to give 0.36 g (15% based on 3-fluoroisatoic anhydride (**41**)) of 2-amino-3-fluorobenzamide **72** as tan crystals. Mp: 175−176 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.59 (m, 2), 1.80 (m, 2), 3.18−3.66 (m, 10), 4.09 (br d, 2, J = 13.3), 4.30 (br s, 2), 6.56 (ddd, J = 5.1, 8.0, 8.0), 7.14 (dd, 1, J = 1.4, 8.0), 7.20 (dd, 1, J = 1.2, 8.0), 7.41 (d, 1, J = 8.0), 7.49 (tm, 1, J = 7.7), 7.62 (tm, 1, J = 7.4), 8.14 (t, 2, J = 6.9), 8.48 (br t, 1, J = 5.6), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 20.68, 26.26, 38.17, 46.41, 50.49, 55.18, 113.99, 114.09, 116.63, 116.87, 117.32, 117.38, 121.24, 123.72, 123.75, 124.05, 124.67, 127.00, 128.17, 137.77, 137.95, 149.63, 152.16, 152.78, 162.27, 168.00, 168.04. Anal. ($C_{22}H_{26}$-FNOS·HCl) C, H, N.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-5-nitrobenzamide Hydrochloride (73). This compound was prepared according to the method described for benzamide **77**, by employing 5-nitroisatoic anhydride (**42**) (1.08 g, 5.17 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 1.0 equiv). The free base was purified by flash chromatography with EtOAc as eluant. The hydrochloride salt was prepared, recrystallized from EtOH/H_2O, and dried in a vacuum oven to give 1.10 g (43%) of 2-amino-5-nitrobenzamide **73** as a yellow solid. Mp: 224−230 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.80 (m, 2), 3.28 (m, 4), 3.46 (br t, 4, J = 12.1), 3.59 (br d, 2, J = 10.2), 4.08 (br d, 2, J = 12.8), 6.82 (d, 1, J = 9.3), 7.48 (t, 1, J = 7.6), 7.60 (t, 1, J = 7.2), 7.80 (br s, 2), 8.03 (dd, 1, J = 2.5, 9.1), 8.13 (t, 2, J = 8.3), 8.52 (d, 1, J = 2.5), 8.80 (t, 1, J = 5.3), 10.72 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.72, 26.17, 38.34, 46.38, 50.48, 55.20, 112.87, 115.85, 121.18, 123.99, 124.61, 125.71, 126.95, 127.35, 128.11, 134.86, 152.11, 155.31, 162.21, 167.21. Anal. ($C_{22}H_{26}N_6O_3S$·HCl) C, H, N.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-5-chlorobenzamide Hydrochloride (74). This compound was prepared according to the method described for compound **77**, by employing 5-chloroisatoic anhydride (**43**) (1.02 g, 5.17 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 1.0 equiv). The free base was purified by flash chromatography with 1:1 EtOAc:hexanes as eluant. The hydrochloride salt was prepared and recrystallized from EtOH/H_2O to give 1.61 g (65%) of 2-amino-5-chlorobenzamide **74** as a white solid. Mp: 173−176 °C. ^{1}H NMR (DMSO-d_6): δ 1.57 (m, 2), 1.78 (m, 2), 3.10−3.68 (m, 12), 4.08 (br d, 2, J = 13.1), 6.74 (d, 1, J = 8.9), 7.18 (dd, 1, J = 2.4, 8.8), 7.48 (tm, 1, J = 7.2), 7.57 (d, 1, J = 2.4), 7.60 (tm, 1, J = 7.2), 8.13 (t, 2, J = 8.6), 8.45 (t, 1, J = 5.3), 10.70 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.64, 26.19, 38.20, 46.35, 50.44, 55.16, 116.75, 118.78, 119.04, 121.18,124.00, 124.61, 126.95, 127.44, 128.12, 131.37, 146.88, 152.11, 162.21, 167.41. Anal. ($C_{22}H_{26}N_5OSCl$·HCl) C, H, N.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-methoxybenzamide Hydrochloride (75). This compound was prepared by the method described for compound **71**. From 3-methoxyisatoic anhydride (**44**) (3.35 g, 0.017 mol) (obtained from 2-amino-3-methoxybenzoic acid by the method described for compound **39**) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (5.33 g, 0.017 mol, 1.0 equiv) was obtained 5.41 g of the product as the free base. A portion of this material (1.94 g) was dissolved in EtOH (10 mL), and HCl (4.4 mL of a 1 N solution in either, 1.0 equiv) was added. The hydrochloride salt was recrystallized from EtOH/2-propanol to give 1.93 g (65%) of 2-amino-3-methoxybenzamide **75** as off-white crystals. Mp: 136−138 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.80 (m, 2), 3.12−3.60 (m, 6), 3.81 (s, 3), 4.09 (br d, 2, J = 12.9), 6.13 (br s, 1), 6.54 (t, 1, J = 8.0), 6.91 (d, 1, J = 7.6), 7.20 (d, 1, J = 7.8), 7.49 (t, 1, J = 7.4), 7.62 (t, 1, J = 7.5), 8.14 (t, 2, J = 6.8), 8.33 (br t, 1, J = 5.4), 10.89 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.68, 27.29, 39.04, 47.38, 51.48, 56.20, 56.54, 112.83, 114.92, 115.40, 120.73, 122.18, 124.98, 125.59, 127.93, 129.11, 140.50, 147.88, 153.09, 163.18, 169.79. MS (CI/CH_4, 50 mA/s): M + 1, base (440). Anal. ($C_{23}H_{29}N_5O_2S$·HCl) C, H, N, S, Cl.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-(methylamino)benzamide Hydrochloride (76).** This compound was prepared according to the method described for benzamide **77**, by employing *N*-methylisatoic anhydride (**45**) (0.92 g, 5.17 mmol) and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.5 g, 5.17 mmol, 1.0 equiv). The free base was purified by flash chromatography with EtOAc as eluant. The hydrochloric salt was prepared, recrystallized from EtOH/ether, and dried in a vacuum oven to give 1.22 g (51%) of 2-(methylamino)benzamide **76** as a pale beige solid. Mp: 169−173 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.81 (m, 2), 2.77 (s, 3), 3.30 (m, 4), 3.48 (br d, 3, J = 13.8), 3.58 (br d, 3, J = 12.9), 4.07 (br d, 2, J = 14.8), 6.56 (t, 1, J = 7.4), 6.63 (d, 1, J = 8.3), 7.29 (t, 1, J = 7.7), 7.48 (t, 1, J = 7.5), 7.57 (d, 1, J = 7.2), 7.61 (d, 1, J = 7.4), 7.64 (br s, 1), 8.13 (t, 2, J = 8.3), 8.41 (br t, 1, J = 5.4), 11.00 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.66, 26.28, 29.33, 38.08, 46.36, 50.44, 55.18, 110.55, 114.03, 115.24, 121.17, 123.99, 124.61, 126.96, 128.11, 128.20, 132.26, 149.91, 152.12, 162.20, 169.12. Anal. ($C_{23}H_{29}N_5OS$·HCl) C, H, N.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)benzamide Hydrochloride (77). Isatoic anhydride (**46**) (0.894 g, 5.48 mmol), EtOH (15.0 mL), and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.59 g, 5.48 mmol, 1.0 equiv) were added to a round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet. the reaction mixture was stirred at room temperature for 22 h. The solvent was removed *in vacuo* to give 2.35 g of a brown oil. The crude material was purified by flash chromatography with 19:1 CH_2Cl_2:MeOH as eluant to give 1.28 g of an orange oil, which became a pale yellow solid upon standing. To a

solution of the free base (0.35 g, 0.855 mmol) in EtOAc and EtOH was added HCl (0.855 mL of a 1 N solution in ether, 1.0 equiv). The resulting hydrochloride salt was recrystallized from 95% EtOH to give 0.230 g (60%) of 2-aminobenzamide **77** as a white solid. Mp: 227−228 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.79 (m, 2), 3.27 (m, 6), 3.47 (br t, 2, J = 12.8), 3.59 (br d, 2, J = 12.4), 4.09 (br d, 2, J = 13.2), 6.41 (br s, 2), 6.51 (ddd, J = 1.1, 7.0, 8.1), 6.69 (dd, 1, J = 1.1, 8.2), 7.13 (ddd, 1, J = 1.5, 7.0, 8.4), 7.48 (m, 2), 7.60 (ddd, 1, J = 1.1, 7.0, 8.0), 8.13 (t, 2, J = 8.4), 8.29 (t, 1, J = 5.5), 10.68 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.64, 26.28, 37.98. 46.35, 50.42, 55.14, 114.49, 114.75, 116.26, 121.14, 123.95, 124.57, 126.10, 126.91, 128.01, 128.07, 131.51, 149.47, 152.06, 162.16, 168.85. Anal. ($C_{22}H_{27}N_5OS$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide Hydroxide (78) and *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-6-hydroxy-2-methoxybenzamide Hydrochloride (79).** *N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2,6-dimethoxybenzamide (**47**) (4.99 g, 9.35 mmol) and anhydrous CH_2Cl_2 (75 mL) were added to a flame-dried 250-mL round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet, and pressure-equalizing addition funnel. To this solution was added HCl (9.25 mL of a 1 N solution in ether, 9.25 mmol, 0.99 equiv) followed by the dropwise addition of boron tribromide (9.35 mL of a 1 N solution in CH_2Cl_2, 9.35 mmol, 1.0 equiv). The reaction mixture was allowed to stir at room temperature for 0.5 h. The reaction mixture was cooled with an ice−water bath, and 1 N NH_4OH (50 mL) was added. The solids were dissolved with the aid of CH_2Cl_2 and H_2O. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic layers were combined, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated to give 3.61 g of the crude product as a sticky yellow residue. The crude free base was purified by flash chromatography with 97:3 CH_2Cl_2:MeOH as eluant to give 2.06 g (R_f = 0.10) of *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide (**78**) as an oil and 1.32 g of a mixture of isomers. This mixture was purified by flash chromatography with EtOAc as eluant to give 0.18 g (R_f = 0.34) of the minor isomer, *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-6-hydroxy-2-methoxybenzamide (**79**), as a tan solid. The hydrochloride salts of each isomer were prepared independently by dissolving the free amine in EtOAc and treating them with HCl (1 equiv of a 1 N solution in ether). The hydrochloride salt of the major isomer was recrystallized from EtOH/H_2O to give 1.67 g (32%) of *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-bromo-2-hydroxy-6-methoxybenzamide hydrochloride (**78**) as a pale pink solid. Mp: 191−192.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.54−1.90 (m, 4), 3.05−3.70 (m, 10), 3.94 (s, 3), 4.07 (br d, 2, J = 12.8), 6.60 (d, 1, J = 9.2), 7.47 (m, 1), 7.60 (m, 1), 7.66 (d, 1, J = 9.0), 8.11 (d, 1, J = 7.6), 8.14 (d, 1, J = 7.9), 8.93 (t, 1, J = 6.2), 10.75 (br s, 1), 14.87 (s, 1). ^{13}C NMR (DMSO-d_6): δ 10.62, 25.95, 38.58, 46.35, 50.44, 55.04, 56.69, 102.30, 103.14, 104.76, 121.17, 123.99, 124.60, 126.95, 128.10, 136.07, 152.10, 158.08, 159.27, 162.21, 168.79. Anal. ($C_{23}H_{27}N_4O_3SBr$·HCl) C, H, N.

The hydrochloride salt of the minor isomer was filtered and dried under high vacuum in an abderholden apparatus to give 76 mg (2%) of *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-bromo-6-hydroxy-2-methoxybenzamide hydrochloride (**79**) as a white solid. Mp: 185−187 °C. ^{1}H NMR (DMSO-d_6): δ 1.60 (m, 2), 1.83 (m, 2), 3.10−3.70 (m, 10), 3.79 (s, 3), 4.09 (m, 2), 6.70 (d, 1, J = 8.8), 7.49 (m, 2), 7.62 (t, 1, J = 7.5), 8.15 (t, 2, J = 7.8), 8.47 (br t, 1, J = 5.2), 10.65 (br s, 1), 10.99 (s, 1). ^{13}C NMR (DMSO-d_6): δ 20.50, 26.17, 38.14, 46.44, 50.55, 55.27, 61.66, 104.70, 114.00, 119.20, 121.19, 124.04, 124.63, 126.99, 128.13, 133.81, 152.13, 154.34, 156.85, 162.24, 165.15. Anal. ($C_{23}H_{27}N_4O_3SB$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-6-hydroxy-2-methoxybenzamide Hydrochloride (80) and *N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-2-hydroxy-6-methoxybenzamide Hydrochloride Hydrate (81).** *N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-2,6-dimethoxybenzamide (**49**) (2.07 g, 4.0 mmol) was monodimethylated according to the method described for compounds **78** and **79**. The two resulting isomers were partially purified by flash chromatography on silica gel with 2:1 EtOAc:hexanes as eluant. Further purification on a Harrison Research chromatotron with 1:1 and 2:1 EtOAc:hexanes as eluant gave a total of 1.07 g of the major isomer, *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-6-hydroxy-2-methoxybenzamide (**80**) (R_f = 0.18 with 2:1 EtOAc:hexanes as eluant), and 0.27 g of the minor isomer, *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-2-hydroxy-6-methoxybenzamide (**81**) (R_f = 0.11 with 2:1 EtOAc:hexanes as eluant), as light orange oils. The hydrochloride salts of each isomer were prepared independently by dissolving the free amine in ether and adding HCl (1 equiv of a 1 N solution in ether).

The hydrochloride salt of the major isomer was recrystallized from EtOH/ether and dried in a vacuum oven to give 0.76 g (35%) of *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-6-hydroxy-2-methoxybenzamide hydrochloride (**80**) as an off-white powder. Mp: 179−181 °C. ^{1}H NMR (DMSO-d_6): δ 1.12 (t, 3, J = 7.3), 1.64 (m, 2), 1.81 (m, 2), 2.52 (m, 3), 3.20−3.60 (m, 9), 3.82 (s, 3), 4.06 (br d, 2, J = 12.3), 7.38 (s, 1), 7.47 (m, 1), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 6.6), 8.83 (br t, 1, J = 5.1), 11.25 (br s, 1), 13.60 (s, 1). ^{13}C NMR (DMSO-d_6): δ 13.69, 20.65, 22.00, 26.04, 38.33, 46.39, 50.46, 55.15, 61.64, 110.73, 115.79, 121.24, 124.05, 124.66, 127.00, 128.16, 129.76, 132.33, 152.03, 152.16, 157.96, 162.27, 167.77 Anal. ($C_{25}H_{31}N_4O_3SCl$·HCl) C, H, N.

The hydrochloride salt of the minor isomer was recrystallized from 95% EtOH and dried in a vacuum oven to give 0.156 g (7%) of *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-chloro-5-ethyl-2-hydroxy-6-methoxybenzamide hydrochloride hydrate (**81**) as fluffy, off-white crystals. Mp: 171−713 °C. ^{1}H NMR (DMSO-d_6): δ 1.15 (t, 3, J = 7.6), 1.62 (m, 2), 1.81 (m, 2), 2.52 (q, 2, J = 7.6), 3.20−3.62 (m, 10), 3.72 (s, 3), 4.08 (br d, 2, J = 12.7), 7.40 (s, 1), 7.47 (t, 1, J = 7.6), 7.60 (t, 1, J = 7.5), 8.12 (t, 2, J = 8.3), 8.78 (br t, 1, J = 5.6), 10.63 (br s, 1), 12.64 (s, 1). ^{13}C NMR (DMSO-d_6): δ 15.77, 21.54, 22.13, 26.99, 39.34, 47.32, 51.40, 56.09, 63.26, 114.02, 117.53, 122.16, 124.97, 125.58, 127.93, 129.09, 129.13, 133.19, 153.08, 154.66, 155.93, 163.20, 168.18. Anal. ($C_{25}H_{31}N_4O_3SCl$·1.25H_2O) C, H, N, H_2O.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-hydroxybenzamide Hydrochloride (82).** 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (3.0 g, 10.4 mmol), triethylamine (1.74 mL, 1.26 g, 12.5 mmol, 1.2 equiv), and CH_2Cl_2 (50 mL) were added to a flame-dried 200-mL three-necked round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and nitrogen inlet. The reaction mixture was cooled in an ice−water bath, and a solution of acetylsalicyloyl chloride (**29**) (2.06 g, 10.4 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 15 min. The reaction mixture was washed with cold saturated $NaHCO_3$. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 5.8 g of the crude material as an orange oi. The crude reaction mixture was purified by flash chromatography with 95:5 CH_2Cl_2:MeOH as eluant. The product (2.93 g) was obtained as a mixture of ((4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)carbamoyl)phenylacetate (**51**) and *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-hydroxybenzamide (**82**). This mixture and MeOH (30.0 mL) were added to a 300-mL round-bottomed flask equipped with a magnetic stirring bar, additional funnel, and nitrogen inlet. A solution of sodium methoxide (38.5 mg, 7.12 mmol, 1.1 equiv) in MeOH (60 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to stir for 1.5 h, neutralized with Dowex resin, filtered, and concentrated to give 2.68 g of the free base as a viscous pale orange oil. To a solution of the free base in EtOAc was added HCl (6.53 mL of a 1 N solution in ether, 1.0 equiv). The resulting hydrochloride salt was recrystallized from EtOH/H_2O to give 2.32 g (50% based on acetylsalicyloyl chloride) of 2-hydroxybenzamide **82** as an off-white solid. Mp: 200−201 °C. ^{1}H NMR (DMSO-d_6): δ 1.63 (m, 2), 1.80 (m, 2), 3.27 (m, 6), 3.47 (br t, 2, J = 12.7), 3.59 (br d, 2, J = 11.3), 4.07 (br d, 2, J = 13.5), 6.89 (m, 2), 7.40 (ddd,

1, J = 1.7, 7.2, 8.8), 7.47 (ddd, 1, J = 1.1, 6.9, 8.1), 7.60 (ddd, 1, J = 1.1, 7.0, 8.1), 7.90 (dd, 1, J = 1.4, 7.9), 8.12 (t, 2, J = 8.4), 8.98 (br t, 1, J = 5.5), 10.80 (br s, 1), 12.68 (s, 1). ^{13}C NMR (DMSO-d_6): δ 20.60, 25.99, 38.38, 46.35, 50.44, 55.06, 115.07, 117.31, 118.43, 121.14, 123.95, 124.57, 126.90, 127.69, 128.07, 133.59, 152.05, 160.09, 162.16, 169.03. Anal. ($C_{22}H_{26}N_4O_2S$·HCl) C, H, N.

4-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)benzamide Hydrochloride (83). *N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-((*tert*-butoxycarbonyl)-amino)benzamide (**60**) (800 mg, 1.57 mmol), anisole (1.5 mL), anhydrous $CHCl_3$ (15 mL), and trifluoroacetic acid (15 mL) were added to a 500-mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet. The reaction mixture was stirred for 0.5 h at room temperature. The solvent was removed *in vacuo* to obtain an oil. The crude oil was dissolved in EtOAc, washed with saturated K_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give a yellow solid. The crude amine was purified by flash chromatography with EtOAc:0.2% triethylamine to give 0.37 g of the amine as an oil. To a solution of the amine in EtOAc and CH_2Cl_2 was added 0.90 mL of 1 N ethereal HCl (1.0 equiv). The solvent was removed *in vacuo*, and the hydrochloride salt was recrystallized from EtOH/H_2O to give 200 mg (29%) of 4-aminobenzamide **83** as a tan solid. Mp: 213.5−214.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.56 (m, 2), 1.77 (m, 2), 3.27 (m, 6), 3.45 (br t, 2, J = 12.5), 3.59 (br d, 2, J = 11.9), 4.08 (br d, 2, J = 13.2), 5.61 (br s, 2), 6.54 (d, 2, J = 8.6), 7.48 (ddd, 1, J = 1.1, 7.1, 8.1), 7.60 (m, 3), 8.12 (m, 3), 10.65 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.65, 26.52, 38.11, 46.37, 50.44, 55.15, 112.43, 121.16, 123.96, 124.58, 126.91, 128.08, 128.62, 151.44, 152.06, 162.18, 166.20. Anal. ($C_{22}H_{27}N_5OS$·HCl) C, H, N.

3-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)benzamide Hydrochloride Hydrate (84). This compound was prepared according to the method described for compound **83**, by employing *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-((*tert*-butoxycarbonyl)amino)benzamide (**61**) (1.77 g, 3.47 mmol), anisole (3.0 mL), anhydrous $CHCl_3$ (30 mL), and trifluoroacetic acid (30 mL). The crude amine was purified by flash chromatography with EtOAc:0.1% trimethylamine followed by EtOAc:0.2% triethylamine to give 1.16 of the free base as an orange oil. The hydrochloride salt was prepared and recrystallized from EtOH/ether to give 0.31 g (20%) of 3-aminobenzamide **84** as a rust-orange solid. Mp: 122−130 °C effervesces. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.80 (m, 2), 3.05−3.75 (m, 10), 4.08 (br d, 2, J = 13.0), 6.10 (br s, 2), 6.79 (d, 1, J = 7.4), 7.13 (m, 3), 7.48 (ddd, 1, J = 1.0, 6.9, 8.1), 7.60 (ddd, 1, J = 1.1, 6.9, 8.1), 8.13 (t, 2, J = 8.4), 8.38 (br t, 1, J = 5.5), 10.77 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.66, 26.35, 38.36, 46.40, 50.49, 55.20, 114.21, 115.93, 117.63, 121.21, 124.05, 124.64, 126.98, 128.14, 128.72, 135.61, 146.36, 152.13, 162.22, 166.77. Anal. ($C_{22}H_{27}N_5OS$·HCl·0.5H_2O) C, H, N, H_2O.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-hydrazinobenzamide Dihydrochloride Hydrate (85).** *N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-(2-(*tert*-butoxycarbonyl)hydrazino)benzamide (**62**) (2.85 g, 5.43 mmol), anhydrous anisole (5 mL), and anhydrous $CHCl_3$ (75 mL) were combined in a 500-mL round-bottom flask. To the stirred pale yellow solution was added trifluoroacetic acid (25 mL). The reaction mixture was allowed to stir under a nitrogen atmosphere for 10 min, and the solution was concentrated *in vacuo*. The residue was transferred to a separatory funnel with the aid of $CHCl_3$ and washed with saturated $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with $CHCl_3$. The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give an orange liquid. The crude product was purified by column chromatography with a gradient eluant of 97−95% CH_2Cl_2 to 3−5% MeOH to give 1.54 g of the free base as a partially solidified yellow oil. The free base (1.41 g, 3.32 mmol) was dissolved in CH_2Cl_2, and 1 N ethereal HCl (6.8 mL, 2.05 equiv) was added. The resulting dihydrochloride salt was recrystallized from EtOH/H_2O/ether to give 1.1 g (40%) of 2-hydrazinobenzamide **85** as a gold yellow solid. Mp: 222−226 °C. ^{1}H NMR (DMSO-d_6): δ 1.62 (m, 2), 1.83 (m, 2), 3.17 (m, 2), 3.29 (q, 2, J = 5.8, 6.6), 3.37 (m, 2), 3.54 (br s, 4), 4.05 (br s, 2), 6.99 (t, 1, J = 7.5), 7.12 (d, 1, J = 8.0), 7.46 (m, 2), 7.58 (t, 1, J = 7.6), 7.73 (dd, 1, J = 1.3, 7.5), 8.06 (br s, 1), 8.09 (d, 1, J = 8.2), 8.13 (d, 1, J = 8.2), 8.78 (t, 1, J = 5.6), 9.18 (s, 1), 10.27 (br s, 3), 11.18 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.62, 26.15, 38.25, 46.40, 50.51, 55.15, 114.43, 118.83, 120.41, 121.24, 124.07, 124.68, 127.01, 128.17, 128.36, 132.07, 145.66, 152.14, 162.30, 167.93. MS (CI/CH_4, 50 mA/s): + 1 (425), base (291). Anal. ($C_{22}H_{28}N_6OS$·2HCl·0.5H_2O) C, H, N, Cl, H_2O.

2-Acetamido-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide Hydrochloride (86). This compound was prepared according to the method described for benzamide **53**, by employing 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (**77**) (1.3 g, 3.17 mmol), triethylamine (0.66 mL, 0.48 g, 4.78 mmol, 1.5 equiv), CH_2Cl_2 (25 mL), and acetyl chloride (0.226 mL, 0.25 g, 3.17 mmol, 1.0 equiv). The reaction mixture was stirred in an ice−water bath for 1 h and allowed to warm to room temperature. The reaction mixture was worked up after 18 h. The free base was purified by flash chromatography with EtOAc:0.1% triethylamine as eluant to give 1.09 g of the free base as an oil. To a solution of the free base (1.04 g, 2.30 mmol) in EtOAc was added 2.30 mL of 1 N ethereal HCl (1.0 equiv). The solvent was removed *in vacuo*, and the hydrochloride salt was recrystallized from EtOH to give 0.859 g (56%) of 2-acetamidobenzamide **86** as a beige solid. Mp: 189.5−190.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.67 (m, 2), 1.84 (m, 2), 2.10 (s, 3), 3.10−3.75 (m, 10), 4.09 (br d, 2, J = 12.9), 7.16 (tm, 1, J = 7.7), 7.49 (t, 2, J = 7.8), 7.62 (t, 1, J = 7.4), 7.78 (dm, 1, J = 7.8), 8.13 (d, 1, J = 7.6), 8.16 (d, 1, J = 7.8), 8.36 (d, 1, J = 8.2), 8.84 (br t, 1, J = 5.2), 10.86 (br s, 1), 11.24 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.61, 24.78, 25.99, 38.40, 46.33, 50.41, 55.08, 120.46, 121.07, 121.16, 122.49, 123.96, 124.58, 126.92, 128.09, 131.68, 138.78, 152.06, 162.17, 168.08, 161.18. Anal. ($C_{24}H_{29}N_5O_2S$·HCl) C, H, N.

Ethyl *N*-(2-(((4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)amino)carbonyl)phenyl)carbamate Hydrochloride (87). 2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (**77**) (1.5 g, 3.66 mmol), triethylamine (0.638 mL, 0.463 g, 4.58 mmol, 1.25 equiv), and anhydrous $CHCl_3$ (10 mL) were added to a flame-dried 50-mL round-bottomed flask. The reaction mixture was placed under N_2 and cooled with an ice−water bath, and a solution of ethyl chloroformate (0.385 mL, 0.437 g, 4.03 mmol, 1.1 equiv) in anhydrous $CHCl_3$ (10 mL) was added dropwise. After the addition of ethyl chloroformate was complete, the ice−water bath was removed and the reaction mixture was allowed to stir at room temperature for 18 h. Additional portions of triethylamine (0.51 mL, 0.37 g, 3.66 mmol, 1.0 equiv) and ethyl chloroformate (0.35 mL, 0.4 g, 3.66 mmol, 1.0 equiv) were added to the reaction mixture. The solution was allowed to stir at room temperature for 4 days. The reaction mixture was transferred to a separatory funnel, CH_2Cl_2 was added, and the solution was washed with saturated $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 1.74 g of the crude product as an orange oil. The free base was purified by flash chromatography with EtOAc:hexanes (2:1):0.1% triethylamine followed by EtOAc:0.1% triethylamine as eluant to give 0.49 g of the free base as an oil. HCl (0.96 mL of 1 N solution in ether, 1.0 equiv) was added to a solution of the free base (0.46 g, 0.96 mmol) in CH_2Cl_2 and EtOAc. The hydrochloride salt was filtered and dried in vacuum oven to give 0.385 g (20%) of ethyl carbamate **87** as a white solid. Mp: 195−195.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.24 (t, 3, J = 7.2), 1.62 (m, 2), 1.83 (m, 2), 3.26 (m, 6), 3.47 (m, 2), 3.61 (m, 2), 4.07 (m, 2), 4.14 (q, 2, J = 7.2), 7.10 (tm, 1, J = 7.7), 7.49 (m, 2), 7.60 (ddd, 1, J = 1.1, 7.0, 8.1), 7.79 (dd, 1, J = 1.5, 7.9), 8.12 (tm, 2, J = 8.4), 8.20 (dd, 1, J = 0.9, 8.3), 8.89 (br t, 1, J = 5.5), 10.85 (br s, 1), 10.97 (s, 1). ^{13}C NMR (DMSO-d_6): δ 14.41, 20.68, 26.01, 38.47, 46.44, 50.53, 55.16, 60.61, 118.62, 119.59, 121.25, 121.70, 124.04, 124.67, 127.00, 128.18, 128.24, 132.18, 139.30, 152.16, 152.91, 162.24, 168.36. Anal. ($C_{25}H_{31}N_5O_3S$·HCl) C, H, N.

***N*-(2-(*N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)-butyl)carbamoyl)phenyl)-L-valinamide Trifluoroacetate Hydrate (88).** 2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (**77**) (2.39 g, 5.84 mmol), anhydrous $CHCl_3$ (60 mL), and 5% aqueous Na_2CO_3 (60 mL) were added to a 300-mL round-bottomed flask. To the two-phase reaction mixture was added a solution of *N*-((9*H*-fluoren-9-ylmethoxy)carbonyl)-L-valyl chloride[28] (3.3 g, 9.22 mmol, 1.58 equiv). The two-phase reaction mixture was allowed to stir for 10 min at room temperature and transferred to a separatory funnel. $CHCl_3$ was added, and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to give 6.48 g of the crude product as a pale yellow oil. This crude material was purified by flash chromatography with 95:5 EtOAc:MeOH as eluant to give 4.5 g (95%) of *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((*N*-((9*H*-fluoren-9-ylmethoxy)carbonyl)-L-valyl)amino)benzamide as a white glass. ^{1}H NMR ($CDCl_3$): δ 1.00 (d, 3, J = 6.9), 1.07 (d, 3, J = 6.8), 1.64 (m, 4), 2.36 (m, 3), 2.62 (m, 4), 3.38 (m, 2), 3.53 (br t, 4, J = 4.8), 4.37 (m, 4), 5.55 (d, 1, J = 8.6), 6.83 (br s, 1), 7.10 (t, 1, J = 7.6), 7.30 (m, 4), 7.48 (t, 4, J = 7.1), 7.66 (t, 2, J = 8.1), 7.82 (m, 4), 8.61 (d, 1, J = 8.3), 11.59 (br s, 1).

This FMOC-protected compound (3.57 g, 4.88 mmol), $CHCl_3$ (110 mL), and 4-(aminomethyl)piperidine (50 mL) were added to a 500-mL round-bottomed flask. The reaction mixture was stirred under nitrogen at room temperature for 0.5 h. The reaction mixture was transferred to a separatory funnel, and $CHCl_3$ (150 mL) was added. The organic layer was washed with H_2O (3 × 250 mL), separated, dried over $MgSO_4$, filtered, and concentrated to give 5.67 g of the crude product as a yellow oil. The free base was purified by column chromatography on silica gel with 85:15 EtOAc:MeOH as eluant to give 2.13 g of the free base as a viscous oil. A portion of the free base (1.17 g) was purified further by semipreparative HPLC (Vydac C-18 column) with 0.1% CF_3CO_2H/H_2O:0.1% CF_3CO_2H/CH_3CN gradient 9:1−1:9. The appropriate fractions were combined, concentrated, dissolved in H_2O and MeOH, and lyophilized to give 0.87 g (48%) of L-valinamide **88** as a white powder. ^{1}H NMR (DMSO-d_6): δ 1.01 (t, 6, J = 6.5), 1.60 (m, 2), 1.77 (m, 2), 2.18 (m, 1), 3.30 (m, 8), 3.61 (m, 2), 3.95 (m, 1), 4.10 (m, 2), 7.25 (t, 1, J = 7.7), 7.48 (tm, 1, J = 7.5), 7.58 (m, 2), 7.76 (d, 1, J = 7.8), 8.13 (t, 2, J = 9.0), 8.24 (d, 1, J = 8.4), 8.40 (br s, 1), 8.89 (br t, 1, J = 4.8), 10.33 (br s, 1), 11.48 (s, 1). ^{13}C NMR (DMSO-d_6): δ 17.96, 18.05, 20.90, 25.92, 29.88, 46.63, 50.67, 55.31, 58.78, 121.26, 121.58, 123.01, 123.95, 124.02, 124.69, 126.97, 128.21, 128.25, 131.83, 137.09, 152.16, 157.69, 158.11, 158.54, 158.96, 162.17, 166.70, 168.00. Anal. ($C_{27}H_{36}N_6O_2S$·2.35CF_3CO_2H·0.75H_2O) C, H, N, F, H_2O.

***N*-(2-(*N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)-butyl)carbamoyl)phenyl)-D-valinamide Trifluoroacetate Hydrate (89).** This compound was prepared according to the method described for compound **88**, by employing 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide (**77**) (2.33 g, 5.7 mmol), *N*-((9*H*-fluoren-9-ylmethoxy)carbonyl)-D-valyl chloride[28] (3.22 g, 9.0 mmol, 1.58 equiv), anhydrous $CHCl_3$ (120 mL), and 5% aqueous Na_2CO_3 (60 mL). The crude intermediate was purified to give 3.42 g (82%) of *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-((*N*-((9*H*-fluoren-9-ylmethoxy)carbonyl)-D-valyl)amino)benzamide as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.01 (d, 3, J = 6.8), 1.07 (d, 3,J = 6.8), 1.64 (m, 4), 2.36 (m, 3), 2.62 (br t, 4, J = 4.5), 3.42 (m, 2), 3.53 (br t, 4, J = 4.8), 4.37 (m, 4), 5.55 (d, 1, J = 8.6), 6.80 (br s, 1), 7.10 (t, 1, J = 7.2), 7.36 (tm, 4, J = 4.4), 7.48 (tm, 4, J = 7.6), 7.67 (t, 2, J = 8.2), 7.80 (m, 4), 8.62 (dm, 1, J = 8.9), 11.58 (br s, 1).

This FMOC-protected intermediate (3.47 g, 4.75 mmol), $CHCl_3$ (100 mL), and 4-(aminomethyl)piperidine (50 mL) were reacted as described for compound **88**. The crude material was purified by column chromatography with 85:15 EtOAc:MeOH to give 1.99 g of the free base as a viscous oil. A portion (0.61 g) of the free base was applied to a semipreparative column, and 0.54 g (57%) of D-valinamide **89** was obtained as a white powder. ^{1}H NMR (DMSO-d_6): δ 1.01 (t, 6, J = 6.5), 1.60 (m, 2), 1.78 (m, 2), 2.18 (m, 1), 3.32 (m, 8), 3.62 (m, 2), 3.95 (m, 1), 4.10 (br d, 2, J = 10.5), 4.56 (br s, 3), 7.24 (t, 1, J = 7.7), 7.48 (t, 1, J = 7.7), 7.58 (m, 2), 7.77 (d, 1, J = 7.5), 8.13 (m, 2), 8.23 (d, 1, J = 8.1), 8.34 (br s, 3), 8.90 (br t, 1, J = 5.3), 10.54 (br s, 1), 11.49 (s, 1). ^{13}C NMR (DMSO-d_6): δ 18.91, 18.97, 21.78, 26.86, 30.80, 47.52, 51.55, 56.21, 59.69, 122.18, 122.51, 123.98, 124.87, 124.95, 125.61, 127.90, 129.12, 129.20, 132.72, 138.00, 153.09, 158.68, 159.11, 159.54, 159.98, 163.12, 167.62, 168.91. Anal. ($C_{27}H_{36}N_6O_2S$·2.35CF_3CO_2H·0.75H_2O) C, H, N, F, H_2O.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,2,2-trifluoroacetamide (93).** 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (6.0 g, 20.7 mmol) and anhydrous CH_2Cl_2 (50 mL) were added to a flame-dried three-necked 250-mL round-bottomed flask equipped with a magnetic stirring bar, thermometer, addition funnel, and nitrogen inlet. The solution was cooled in an ice−water bath, and a solution of trifluoroacetic anhydride (4.40 mL, 6.53 g, 31.1 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) was added dropwise over a 0.5-h period. The reaction mixture was allowed to stir for 2 h. Saturated K_2CO_3 (50 mL) was slowly added to the cold reaction mixture. The reaction mixture was transferred to a separatory funnel, and the solution was extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 6.87 g (86%) of trifluoroacetamide **93** as an orange oil. The crude material was used without further purification. ^{1}H NMR ($CDCl_3$): δ 1.71 (br s, 4), 2.51 (br t, 2, J = 6.2), 2.71 (t, 4, J = 4.8), 3.41 (m, 2), 3.59 (t, 4, J = 4.9), 7.36 (t, 1, J = 7.9), 7.49 (t, 1, J = 7.9), 7.83 (d, 1, J = 8.0), 7.90 (d, 1, J = 7.9).

***N*-(4-(4-(1,2-Benzisothiazol-3-yl-1-piperazinyl)butyl)-*N*-methyl-2,2,2-trifluoroacetamide (94).** Sodium hydride (0.587 g, 19.6 mmol) as an 80% dispersion in oil was added to a flame-dried three-necked 250-mL round-bottomed flask equipped with a rubber septum, magnetic stirring bar, addition funnel, and nitrogen inlet. The sodium hydride was washed three times with hexanes, and anhydrous THF (30.0 mL) was added. The suspension was cooled in an ice−water bath, and a solution of *N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,2,2-trifluoroacetamide (**93**) (6.87 g, 17.8 mmol) in anhydrous THF (30.0 mL) was slowly added over a 35-min period. The ice−water bath was removed, and a solution of methyl iodide (1.1 mL, 2.53 g, 17.8 mmol) in anhydrous THF (20 mL) was added dropwise. The yellow-orange solution was allowed to warm to room temperature and stir for 4 days. The excess NaH was quenched with water (15 mL), and the THF was removed *in vacuo*. The residue was partitioned between H_2O and CH_2Cl_2. The two phases were separated, and the aqueous phase was extracted two additional times with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give the crude product as an orange oil. The crude free base was purified by flash chromatography with EtOAc as eluant to give 4.55 g (64%) of *N*-methyltrifluoroacetamide **94** as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.59 (m, 2), 1.71 (m, 2), 2.47 (t, 2, J = 7.0), 2.68 (m, 4), 3.04 and 3.14 (2 s, 3, NCH_3 tautomers), 3.45 (m, 2), 3.58 (m, 4), 7.36 (t, 1, J = 7.2), 7.48 (t, 1, J = 7.5), 7.82 (d, 1, J = 7.7), 7.91 (d, 1, J = 8.0).

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-*N*-methylbenzamide Hydrochloride (96).** Sodium hydride (1.67 g, 55.7 mmol, 2.5 equiv of an 80% oil dispersion) was added to a flame-dried three-necked 250-mL round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and N_2 inlet. The sodium hydride was washed with hexanes (3×), and the waste hexanes were removed each time with a pipet. To the washed sodium hydride was added anhydrous DMF (20.0 mL), and the resulting suspension was cooled in an ice bath. To the cooled reaction mixture was added a solution of *N*-methylbenzamide (**90**) (3.0 g, 22.2 mmol, 1.0 equiv) in anhydrous DMF (15.0 mL). The reaction mixture was allowed to stir until hydrogen evolution ceased, and 1-bromo-4-chlorobutane (2.81 mL, 4.19 g, 24.4 mmol, 1.1 equiv) was added dropwise. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 0.5 h, the reaction mixture was cooled in an ice bath and the excess NaH was quenched with distilled H_2O (10 mL). The solvent was removed *in vacuo*, and the residue was partitioned between saturated aqueous K_2CO_3 and CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 6.17

g of a yellow oil. The crude material was purified by flash chromatography with 1:2 hexanes:ethyl acetate as eluant to give 3.02 g (60%) of chloride **91** as a pale yellow oil. Chloride **91** (1.5 g, 6.65 mmol), 3-(1-piperazinyl)-1,2-benzisothiazole (1.60 g, 7.3 mmol, 1.1 equiv), triethylamine (1.39 mL, 1.01 g, 9.98 mmol, 1.5 equiv), and acetonitrile (25.0 mL) were added to a 100-mL round-bottomed flask equipped with a magnetic stirring bar, condenser, and N_2 inlet. The reaction mixture was heated to reflux under nitrogen overnight. The solvent was removed *in vacuo*, and the residue was partitioned between saturated aqueous potassium carbonate and ethyl acetate. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 3.64 g of an orange oil. The crude material was purified by flash chromatography with 2:1 ethyl acetate:hexanes:0.1% triethylamine followed by ethyl acetate: 0.1% triethylamine as eluant to give 1.40 g of a yellow oil. The free base was taken up in ethyl acetate, and HCl (3.53 mL of a 1 N solution in ether, 1.0 equiv) was added. The resulting salt was recrystallized from EtOH/Et_2O to give 0.76 g (26%) of the title compound as a white solid. Mp: 151−154 °C. ^{1}H NMR (DMSO-d_6): δ 1.57−1.83 (m, 4), 2.98 (m, 4), 3.26 (m, 4), 3.55 (m, 5), 4.07 (br d, 2, J = 12.6), 7.44 (m, 6), 7.60 (t, 1, J = 7.3), 8.13 (t, 2, J = 8.1), 11.07 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.29, 23.68, 36.91, 45.74, 46.27, 50.40, 55.22, 121.14, 123.95, 124.56, 129.15, 136.70, 152.06, 162.17, 170.15. Anal. ($C_{23}H_{28}N_4OS$·HCl) C, H, N.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-*N*-methylbenzamide Hydrochloride (97). *N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-*N*-methyl-2,2,2-trifluoroacetamide (**94**) 2.0 g, 5.0 mmol), MeOH (50 mL), and 20.0 mL of K_2CO_3 (7% aqueous solution) were added to a 250-mL round-bottomed flask equipped with a magnetic stir bar. The reaction mixture was allowed to stir at room temperature for 6 h. The MeOH was removed *in vacuo*, and the solution was extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give 1.41 g (93%) of 3-(4-(4-(methylamino)butyl)-1-piperazinyl)-1,2-benzisothiazole (**95**) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.45 (m, 1), 1.55 (m, 4), 2.45 (s, 5), 2.69 (m, 6), 3.58 (m, 4), 7.36 (tm, 1, J = 7.7), 7.48 (tm, 1, J = 7.4), 7.83 (d, 1, J = 8.6), 7.93 (d, 1, J = 8.6).

This amine (1.4 g, 4.6 mmol), isatoic anhydride (0.750 g, 4.6 mmol, 1.0 equiv), and EtOH (25.0 mL) were added to a 100-mL round-bottomed flask equipped with a magnetic stir bar and nitrogen inlet. The reaction mixture was placed under a N_2 atmosphere and allowed to stir at room temperature for 20 h and to stand for 6 h without stirring. The reaction mixture was concentrated *in vacuo* to give the crude product as a brown-orange liquid. The free base was purified by flash chromatography with EtOAc:0.1% triethylamine as eluant to give 1.06 g of the free base. To a solution of the free base (1.06 g, 2.50 mmol) in EtOAc was added 2.5 mL of 1 N ethereal HCl (1.0 equiv). The solvent was removed *in vacuo*, and the solid was recrystallized from EtOH and ether to give 0.625 g (30%) of *N*-methylbenzamide **97** as a tan solid. Mp: 188−189 °C. ^{1}H NMR (DMSO-d_6): δ 1.61 (br s, 4), 2.93 (s, 3), 2.95−3.72 (m, 10), 4.07 (br d, 2, J = 12.0), 5.13 (br s, 2), 6.58 (td, 1, J = 7.4, 1.1), 6.73 (dd, 1, J = 0.8, 8.1), 7.02 (dd, 1, J = 1.4, 7.7), 7.09 (ddd, 1, J = 1.7, 7.3, 8.0), 7.48 (ddd, 1, J = 1.0, 7.1, 7.9), 7.60 (ddd, 1, J = 1.0, 6.9, 8.0), 8.13 (t, 2, J = 8.2), 10.85 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.36, 24.20, 46.34, 50.40, 55.13, 115.50, 120.26, 121.16, 123.97, 124.58, 126.92, 127.36, 128.09, 129.69, 145.35, 152.06, 162.18, 169.86. Anal. ($C_{23}H_{29}N_5OS$·HCl) C, H, N.

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