Articles

Synthesis and Evaluation of Heterocyclic Carboxamides as Potential Antipsychotic Agents

Mark H. Norman,*,† Frank Navas III,† James B. Thompson,† and Greg C. Rigdon‡

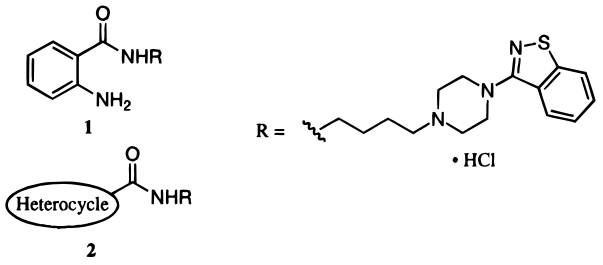
Divisions of Chemistry and of Pharmacology and Molecular Therapeutics, Glaxo Wellcome Inc., Research Triangle Park, North Carolina 27709

Received May 6, 1996⊗

Heterocyclic analogues of 1192U90, 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)benzamide hydrochloride (**1**), were prepared and evaluated as potential antipsychotic agents. These analogues were evaluated *in vitro* for their binding to the dopamine D_2, serotonin 5-HT_2, and serotonin 5-HT_{1a} receptors and *in vivo* for their ability to antagonize the apomorphine-induced climbing response in mice. Nine different types of heterocyclic carboxamides were studied in this investigation (*i.e.*, pyridine-, thiophene-, benzothiophene-, quinoline-, 1,2,3,4-tetrahydroquinoline-, 2,3-dihydroindole-, indole-, benzimidazole-, and indazolecarboxamides). Two derivatives exhibited potent *in vivo* activities comparable to **1**: 3-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide (**16**) and 3-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-thiophenecarboxamide (**29**). Furthermore, these derivatives were found to be much less active in behavioral models predictive of extrapyramidal side effects than in the mouse climbing assay, which predicts antipsychotic activity. Carboxamides **16** and **29** were selected for further evaluation as potential backup compounds to **1**.

Introduction

We recently described the discovery of the potential atypical antipsychotic 1192U90, 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride (**1**).[1] This *o*-amino benzamide is a potent and orally active dopamine D_2 and serotonin 5-HT_2 antagonist as well as a serotonin 5-HT_{1a} agonist.[2] The combination of potent serotonin 5-HT_2 antagonism with moderate dopamine D_2 antagonism is a profile that has been suggested to give drugs like clozapine and risperidone their unique clinical profiles.[3] We postulate that the additional 5-HT_{1a} agonist activity of 1192U90 (**1**) would be beneficial in helping to relieve the anxiety that can often trigger psychotic episodes. In behavioral models[4] and chronic electrophysiological tests,[2] **1** demonstrated activities that indicate it would be efficacious as an antipsychotic agent and have a low propensity to cause extrapyramidal side effects. Due to its superior pharmacological profile, **1** was selected for further development and has recently been tested in phase I clinical trials. We have continued our investigations by expanding the structure−activity relationships of this series to include heterocyclic carboxamides of the general structure **2**. Several heterocycles were prepared and evaluated in this study including pyridine-, thiophene-, benzothiophene-, quinoline-, 1,2,3,4-tetrahydroquinoline-, 2,3-dihydroindole-, indole-, benzimidazole-, and indazole-derived amides. Pyridine and thiophene derivatives were identified with potentreceptor binding affinities and excellent *in vivo* profiles in behavioral models.



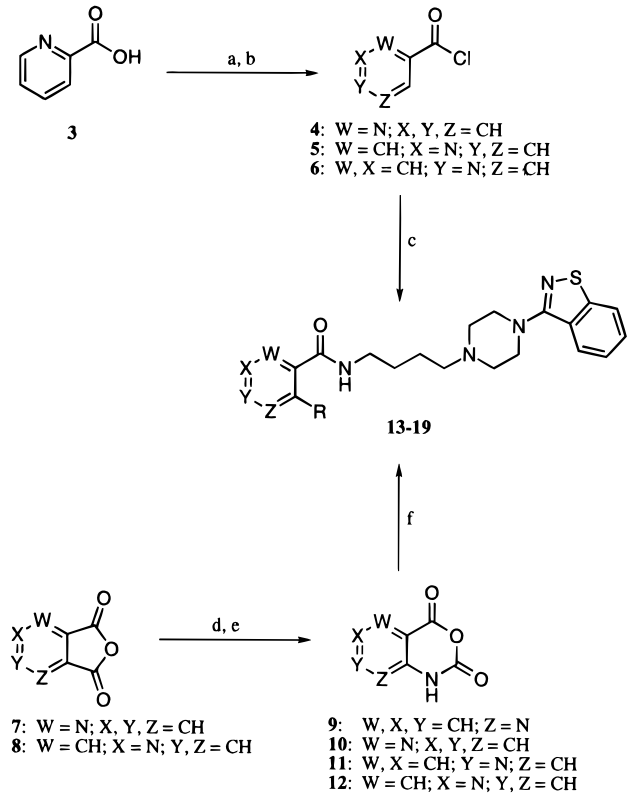
Chemistry

The two general synthetic routes employed to prepare pyridinecarboxamides **13**−**19** are outlined in Scheme 1. The first method involved the treatment of either picolinoyl chloride (**4**), nicotinoyl chloride (**5**), or isonicotinoyl chloride (**6**) with 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole[5] in dichloromethane to provide pyridinecarboxamides **13**−**15**, respectively. Picolinoyl chloride (**4**) was obtained by the reaction of the potassium salt of picolinic acid (**3**) with oxalyl chloride.[6] Nicotinoyl chloride (**5**) and isonicotinoyl chloride (**6**) were obtained from commercial suppliers. Pyridine carboxamides **16**−**19**, which contain an *o*-amino substituent, were prepared from the appropriate azaisatoic anhydrides **9**−**12** by the second route shown in Scheme 1. Treatment of 2,3-pyridinecarboxylic anhydride (**7**) with azidotrimethylsilane provided a 2:1 mixture of 3- and 6- azaisatoic anhydrides **9** and **10**, respectively.[7,8] Analogously, when 3,4-pyridinecarboxylic anhydride (**8**)

* To whom correspondence should be addressed. Current address: Amgen, Small Molecule Drug Discovery, 1840 DeHavilland Dr, Thousand Oaks, CA 91320-1789.
† Division of Chemistry.
‡ Division of Pharmacology and Molecular Therapeutics.
⊗ Abstract published in *Advance ACS Abstracts,* October 15, 1996.

S0022-2623(96)00337-8 CCC: $12.00

Scheme 1[a]



[a] Reagents: (a) KOH, H_2O; (b) oxalyl chloride, benzene; (c) 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, CH_2Cl_2, Et_3N, O °C; (d) $(CH_3)_3SiN_3$, $CHCl_3$; (e) CH_3CN, reflux; (f) 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, THF, room temperature.

was used as the starting material in this nitrene insertion reaction, a 1:l mixture of 4-azaisatoic anhydride (**11**) and 5-azaisatoic anhydride (**12**) was obtained. The azaisatoic anhydride mixtures were condensed with 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole in tetrahydrofuran at room temperature to give the corresponding target pyridinecarboxamides as isomeric mixtures, **16**/**19** and **17**/**18**. The isomeric carboxamides were separated by flash chromatography, treated with ethereal hydrogen chloride, and isolated as their hydrochloride salts.

The position of the nitrogen in each of the four pyridine isomers was easily determined by correlating the experimental ^{13}C NMR chemical shift values of **16** with the theoretical ^{13}C NMR chemical shifts, obtained using the ^{13}C NMR chemical shift prediction module available with the ChemIntosh software program.[9] The experimental ^{13}C NMR chemical shift values are indicated next to the appropriate carbons in Figure 1, and the corresponding theoretical ^{13}C NMR chemical shifts are shown in parentheses. In addition to these ^{13}C NMR correlations, further confirmation of the assignments was obtained from heteronuclear multibond correlation experiments conducted on the free amines. For example, the amide carbonyl carbons in compounds **17** and **18** exhibited three-bond correlations to the *ortho*-aromatic protons. This correlation is indicated by the arrows illustrated in Figure 1. In compound **17**, the *ortho*-proton is adjacent to the pyridine nitrogen and appears as a singlet at 8.60 ppm, while the corresponding *ortho*-proton in compound **18** is coupled with the adjacent *meta*-proton resulting in a doublet at 7.15 ppm.

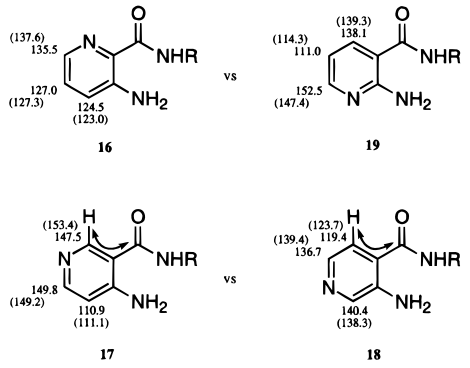
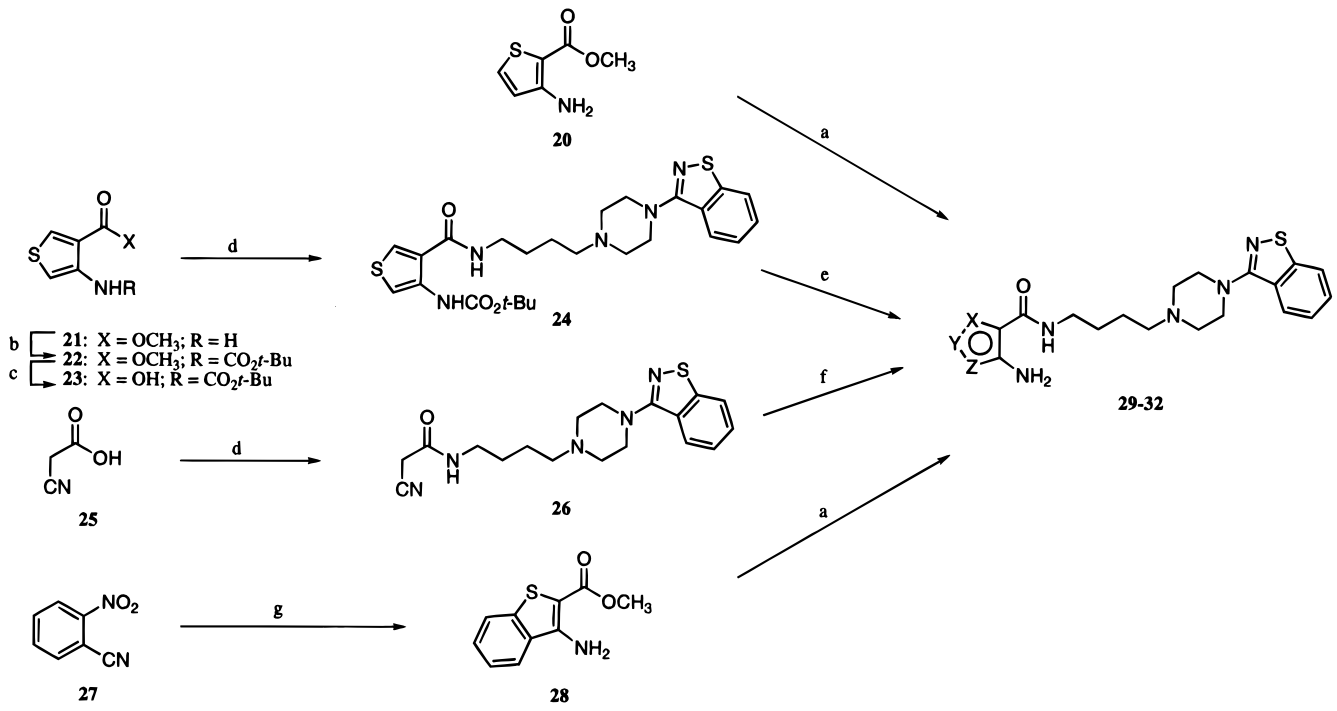


Figure 1. ^{13}C NMR chemical shift values of pyridinecarboxamides **16**−**19** correlated with theoretical ^{13}C NMR values that are shown in parentheses. Arrows indicate the key three-bond heteronuclear correlations observed in the HMBC spectra of compounds **17** and **18**.

Thiophenecarboxamides **29**−**31** and benzothiophenecarboxamide **32** were prepared as summarized in Scheme 2. Condensation of methyl 3-amino-2-thiophenecarboxylate (**20**) with 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole using the trimethylaluminum procedure for aminolysis of esters reported by Weinreb *et al.* provided 3-amino-2-thiophenecarboxamide **29**.[10,11] Attempts to employ the same coupling procedure using the analogous thiophene ester **21** were unsuccessful. Therefore, an alternative method was investigated to prepare the targeted carboxamide **30**. Methyl 4-aminothiophene-3-carboxamide (**21**) was treated with di-*tert*-butyl dicarbonate to provide carbamate **22**. Carboxamate−carboxamide **24** was obtained by the hydrolysis of ester **22** with sodium hydroxide to give acid **23** followed by coupling **23** and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole with 1,3-dicyclohexylcarbodiimide (DCC) in dimethylformamide. Hydrolysis of carbamate **24** with trifluoroacetic acid provided 4-amino-3-thiophenecarboxamide **30**. The final thiophene isomer, 2-amino-3- thiophenecarboxamide **31**, was prepared in two steps from cyanoacetic acid (**25**). A DCC coupling of **25** with 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole provided cyanoacetamide **26** in good yield. The thiophene ring of **31** was constructed by the reaction of cyanoacetamide **26** with 1,4-dithiane-2,5-diol and triethylamine in ethanol.[12] This thiophene isomer, wherein the sulfur of the thiophene ring is adjacent to the aromatic amino group, was unstable to acid and therefore was isolated and evaluated as its free base. Due to the high potency of the 3-amino-2-thiophenecarboxamide isomer **29** (*vide infra*), we prepared the corresponding 3-aminobenzothiophene-2-carboxamide **32**. Treatment of 2-nitrobenzonitrile (**27**) with methyl thioglycolate in DMF provided methyl 3-aminobenzo[*b*]thiophene-2-carboxylate (**28**).[13] Carboxamide **32** was prepared from **28** by employing the trimethylaluminum-mediated coupling as described previously for the preparation of thiophenecarboxamide **29**.

Scheme 3 outlines the synthesis of the seven remaining heterocyclic carboxamides. The final step, common to each derivative, involved the DCC coupling of an appropriate heterocyclic acid with 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole. Quinolinecarboxylic acid (**34**) and indole-3-carboxylic acid (**48**) were obtained from commercial suppliers, while the remaining heterocyclic acids were prepared by a variety of methods. Hydrogenation of **34** over platinum oxide provided

Scheme 2[a]



[a] Reagents: (a) $Al(CH_3)_3$, 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, $CHCl_3$, 50 °C; (b) Boc anhydride, dioxane, Na_2CO_3, room temperature; (c) NaOH, EtOH, 45 °C; (d) 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, DCC, DMF, HOBT; (e) TFA, anisole, $CHCl_3$; (f) 1,4-dithiane-2,5-diol, EtOH, Et_3N, 60−65 °C; (g) methyl thioglycolate, KOH, DMF, room temperature.

1,2,3,4-tetrahydro-8-quinolinecarboxylic acid (**38**) in 99% yield.[14] The homologous derivative, indoline-7-carboxylic acid (**37**), was prepared in three steps from indoline (**33**) by modifications of the procedure reported by Welstead *et al.*[15] In this method, indoline (**33**) was acylated with oxalyl chloride to provide 2-(2,3-dihydro-1*H*-indol-1-yl)glyoxyloyl chloride (**36**). Employing the procedure as previously reported, we found that an unexpectedly high percentage of the bis-indole adduct was obtained. Formation of this side product was eliminated by increasing the ratio of oxalyl chloride to indole and employing CH_2Cl_2 as the solvent.

Indolinecarboxylic acid **37** was obtained by cyclization of acid chloride **36** with aluminum chloride followed by oxidation of the resulting product, 4,5-dihydropyrrolo-[3,2,1-*hi*,*l*]indoline-1,2-dione, with sodium hydroxide and hydrogen peroxide. In addition to being used in the synthesis of the target dihydroindolecarboxamide **39**, acid **37** served as the precursor to the corresponding unsaturated analogue **43**. Indolecarboxylic acid **43** was obtained by the oxidation of **37** with 10% palladium on carbon in refluxing xylenes.[16] Catalytic hydrogenation of 3-nitroanthranilic acid (**41**) followed by treatment of the resulting diamine with formic acid provided benzimidazole-7-carboxylic acid (**42**) in good yield.[17] Indazole-3-carboxylic acid (**47**), the final intermediate required to prepare carboxamide **49**, was obtained in two steps from isatin (**46**) by the method of Synder and co-workers.[18]

Pharmacology

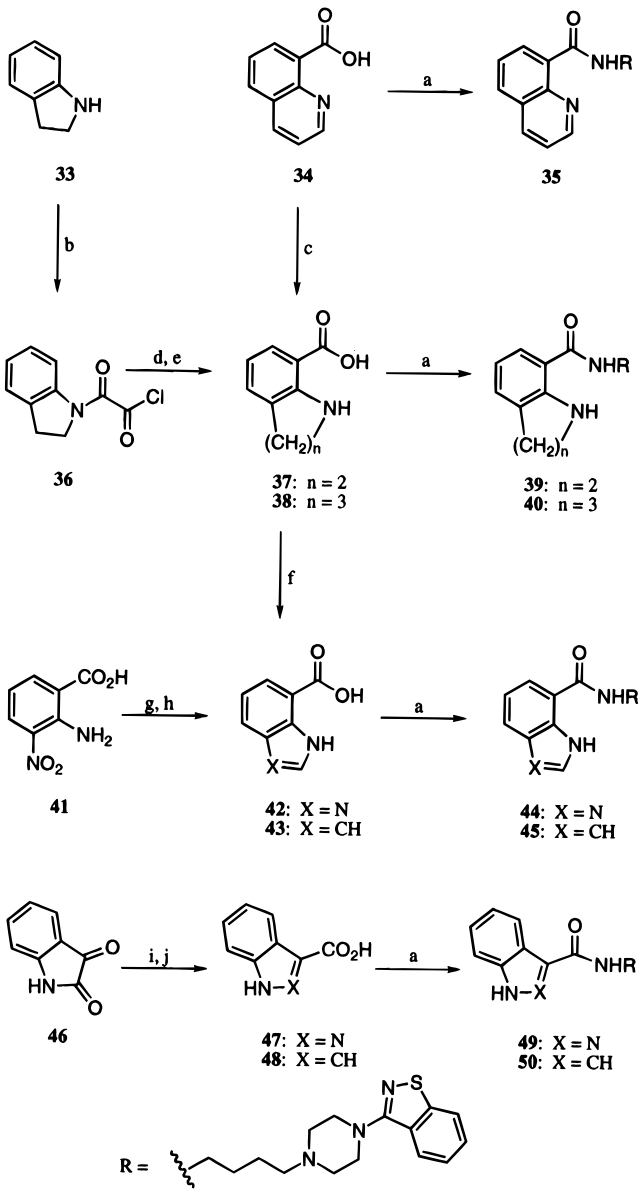
The target heterocyclic carboxamides were examined *in vitro* for their binding affinities to dopamine D_2, serotonin 5-HT_2, and serotonin 5-HT_{1a} receptors. Affinities for the dopamine site were measured by the ability of the compounds to displace [^{3}H]raclopride from the D_2 receptor isolated from the striata of male Sprague−Dawley rats.[5,19] Serotonergic 5-HT_{1a} and 5-HT_2 binding affinities were determined by displacement of [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]-8-OH-DPAT) and [^{3}H]ketanserin, respectively.[5,20,21] Since it has been postulated that compounds that bind to 5-HT_2 receptors more potently than to D_2 receptors are likely to be atypical neuroleptics,[22] the D_2/5-HT_2 receptor binding ratios (IC_{50}'s) were calculated. In addition to examining their *in vitro* binding profiles, the compounds were also evaluated *in vivo* for their ability to antagonize the apomorphine-induced climbing response in mice.[5,23] Antagonism of this response indicates dopamine antagonism in the mesolimbic dopamine system, which is believed to be dysfunctional in schizophrenic patients. As a second phase of the biological evaluation, the most potent derivatives were tested in two assays designed to assess potential extrapyramidal side effect liability: antagonism of apomorphine-induced stereotypy and induction of catalepsy.[5]

Results and Discussion

The compounds have been divided into three general classes, and the biological results are shown in Table 1 (pyridines), Table 2 (thiophenes), and Table 3 (fused bicyclic heterocycles). The corresponding biological data obtained for risperidone, clozapine, and 1192U90 (**1**) are also included in Table 1 for comparison.

In general, the receptor binding activities of pyridinecarboxamides **13**−**19** were similar to that of 1192U90 (**1**). Binding affinities (IC_{50}) remained high (1.5−47 nM) at all three receptors with only slight variations being noted (*e.g.*, D_2 affinities increased for compounds **17** and **19**). All of the pyridine analogues displayed D_2/5-HT_2 ratios > 1; however, the highest D_2/5-HT_2 ratios were obtained with the 2- and 3-pyridinecarboxamides **13** and

Scheme 3[a]



[a] Reagents: (a) 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole, DCC, DMF, HOBT; (b) oxalyl chloride, CH_2Cl_2, room temperature; (c) $PtO_2 \cdot xH_2O$, EtOH, H_2; (d) $AlCl_3$, 100−120 °C; (e) NaOH, H_2O_2, room temperature; (f) Pd−C, xylenes, reflux; (g) H_2, Pd−C, NaOH; (h) HCl, HCO_2H, reflux; (i) NaOH, H_2O, $NaNO_2$, 50−60 °C; (j) H_2SO_4, $SnCl_2 \cdot 2H_2O$, HCl.

14, respectively. Compounds **13** and **14** also retained good oral activity in the mouse climbing assay, while the corresponding 4-pyridinecarboxamide **15** was less active. Mixed results were obtained when the *o*-amino substituent was introduced to the pyridine nucleus. The 2-amino-6-aza analogue **16** was approximately 2 times as active as **1** in the mouse climbing assay when administered orally (5.7 vs 10.1 mg/kg, respectively); however, *in vivo* activity diminished with the 5-, 4-, and 3-aza analogues **17**−**19**.

Biological activities of thiophenecarboxamides **29**−**32** are shown in Table 2. The most potent compound in this series was the 3-amino-2-thiophenecarboxamide analogue **29**, which was equipotent to 1192U90 (**1**) in the mouse climbing assay. As in the pyridinecarboxamide series, the derivative containing the heteroatom adjacent to the amide carbonyl provided optimum activity (*i.e.*, thiophenecarboxamide **29**). Increased serotonin 5-HT_2 binding affinity was observed with the corresponding benzothiophene derivative **32**; however, oral *in vivo* potency was diminished with this derivative.

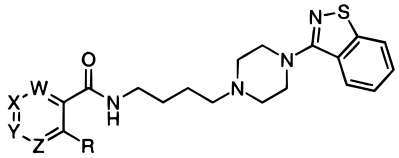
Table 3 shows the results of the final seven bicyclic heterocycles examined in the study. Compounds **35**, **39**, **40**, **44**, and **45** were designed to investigate the effect of altering the nature of the *o*-amino substituent of **1**. This set of compounds consisted of analogues where the *o*-amino group of **1** was incorporated into a ring that was connected to the 3-position of the benzamide nucleus. As observed in the pyridine- and thiophenecarboxamide series, potent receptor binding affinities at all of the target receptors were maintained and good D_2/5-HT_2 ratios were observed. Unfortunately, incorporation of the *o*-amino group into a fused heterocyclic ring resulted in decreased *in vivo* activities. There was surprisingly little difference in the activities of quinolinecarboxamide **35** and indolecarboxamide **45** with their corresponding saturated counterparts, tetrahydroquinolinecarboxamide **40** and dihydroindolecarboxamide **39**, respectively. Introduction of the second nitrogen into the fused ring was also detrimental to *in vivo* activity (*e.g.*, benzimidazole **44**). The last two derivatives, indazolecarboxamide **49** and indolecarboxamide **50**, contain heterocycles common to compounds studied as serotonin 5-HT_3 receptor antagonists.[24] While these compounds showed potent affinities to the serotonin receptors, they were not very active *in vivo*. As before, however, the derivative containing the heteroatom adjacent to the amide carbonyl gave the best *in vivo* activity (*i.e.*, indazolecarboxamide **49** vs indolecarboxamide **50**).

The most potent derivatives in the mouse climbing assay, pyridinecarboxamide **16** and thiophenecarboxamide **29**, were tested for their abilities to antagonize apomorphine-induced stereotypy and to induce catalepsy in mice. The results obtained for compounds **16** and **29** as well as the reference standards are reported in Table 4. The side effect to desired effect ratios were calculated as a measure of the compounds' potential selectivity. Although less selective than 1192U90 (**1**), the heterocyclic analogues **16** and **29** showed excellent selectivity ratios that were equal or superior to those of risperidone and clozapine. These results suggest that compounds **16** and **29** may be useful for the treatment of schizophrenia and may have a low propensity to induce extrapyramidal side effects. Further evaluations will be necessary to determine the potential of this series.

Conclusion

Several heterocyclic analogues of 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)benzamide hydrochloride (**1**) were prepared and evaluated for their potential antipsychotic activity. These heterocyclic derivatives retained potent receptor binding affinities at dopamine D_2 and serotonin 5-HT_2 and 5-HT_{1a} receptors and possessed D_2/5-HT_2 ratios > 1. Compounds in the pyridine- and thiophenecarboxamide series were, in general, more active *in vivo* than the fused bicyclic heterocyclic analogues. A preference was observed for derivatives containing a heteroatom *ortho* to the amide carbonyl (*i.e.*, compounds **16**, **29**, and **49**). Two analogues, pyridinecarboxamide **16** and thiophene-

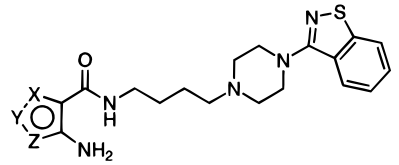
Table 1. *In Vitro* and *in Vivo* Biological Activities of Reference Standards and Pyridinecarboxamides **13**−**19**



						receptor binding[b] IC_{50} (nM)				antagonism of apomorphine-induced mouse climbing ED_{50} (mg/kg)[d]	
compd no.[a]	W	X	Y	Z	R	D_2	5-HT_2	5-HT_{1a}	D_2/5-HT_2[c]	ip	po
risperidone						23	1.5	430	15	0.3	0.9
clozapine						290	28	2000	10	26.2[e]	22.5[f]
1	CH	CH	CH	CH	NH_2	32	3.3	3.8	10	1.5[g]	10.1[h]
13	N	CH	CH	CH	H	24	1.5	2.8	16	<25	16.6
14	CH	N	CH	CH	H	47	2.9	4.9	16	5.2	15.5
15	CH	CH	N	CH	H	25	2.3	6.6	11	4.6	34.0
16	N	CH	CH	CH	NH_2	24	8.3	3.8	3	1.1	5.7
17	CH	N	CH	CH	NH_2	4.7	3.1	5.1	2	>25	
18	CH	CH	N	CH	NH_2	16	1.5	7.0	11	<25	19.5
19	CH	CH	CH	N	NH_2	7.8	1.5	3.3	5	6.4	17.1

[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 5. [e] 95% confidence limits = 9.4−73.2 mg/kg. [f] 95% confidence limits = 12.8−39.8 mg/kg. [g] 95% confidence limits = 0.7−4.2 mg/kg. [h] 95% confidence limits = 5.2−19.3 mg/kg.

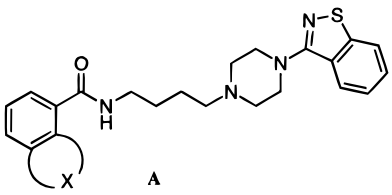
Table 2. *In Vitro* and *in Vivo* Biological Activities of Reference Standards and Thiophenecarboxamides **29**−**32**



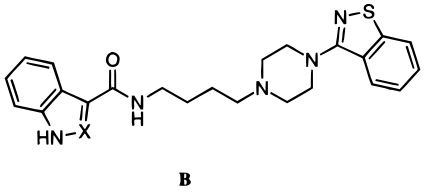
				receptor binding[b] IC_{50} (nM)				antagonism of apomorphine-induced mouse climbing ED_{50} (mg/kg)[d]	
compd no.[a]	X	Y	Z	D_2	5-HT_2	5-HT_{1a}	D_2/5-HT_2[c]	ip	po
29	S	CH	CH	9.6	1.3	1.3	7.4	0.9	9.7
30	CH	S	CH	6.0	2.5	3.5	2.4	1.7	12.6
31	CH	CH	S	11	2.3	2.0	4.8	>25	
32	S			5.8	0.85	5.8	6.8	2.2	51.6

[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 5.

Table 3. *In Vitro* and *in Vivo* Biological Activities of Heterocyclic Amides **35**, **39**, **40**, **44**, **45**, **49**, and **50**



A



B

			receptor binding[b] IC_{50} (nM)				antagonism of apomorphine-induced mouse climbing ED_{50} (mg/kg)[d]	
compd no.[a]	structure	X	D_2	5-HT_2	5-HT_{1a}	D_2/5-HT_2[c]	ip	po
35	A	−CH=CH−CH=N−	14	2.4	4.3	6	<25	54.4
39	A	$-CH_2CH_2NH-$	34	3.4	4.3	10	2.6	18.6
40	A	$-CH_2CH_2CH_2NH-$	28	2.4	1.9	12	<25[e]	
44	A	−N=CHNH−	7.6	0.29	4.2	26	>25	
45	A	−CH=CHNH−	28	1.2	2.7	23	<25[f]	
49	B	−N−	2.2	0.35	3.6	6	<25	31.8
50	B	−CH−	14	1.3	5.8	11	>25	

[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 5. [e] 75% inhibition at 25 mg/kg. [f] 62% inhibition at 25 mg/kg.

carboxamide **29**, were identified with potent activities in the apomorphine-induced mouse climbing assay (ED_{50}'s = 5.7 and 9.7 mg/kg, po, respectively). Significantly higher doses of these compounds were required to induce catalepsy or inhibit apomorphine-induced stereotypies, thereby indicating a low extrapyramidal

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

	antagonism of apomorphine-induced				
compd no.[a]	mouse climbing[b] ED_{50} (mg/kg, po)	stereotypy (mouse)[b] ED_{50} (mg/kg, po)	induction of catalepsy (mouse)[b] ED_{50} (mg/kg, po)	stereotypy[c] / climbing	catalepsy[d] / climbing
risperidone	0.9	3.2	1.4	4	2
clozapine	22.5	78.8[e]	161[f]	4	7
1	10.1	91.1[g]	192[h]	9	19
16	5.7	27.3	45.1	5	8
29	9.7	57.9	69.3	6	7

[a] Hydrochloride salts. [b] For experimental protocol, see ref 5. [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 = 56.1−111 mg/kg. [f] 95% confidenence limits = 98.7−263 mg/kg. [g] 95% confidence limits = 17.6−472 mg/kg. [h] 95% confidence limits = 98.4−376 mg/kg.

side effect liability. Based on these preliminary results, compounds **16** and **29** were selected for further pharmacological studies to evaluate them as potential backup compounds to *o*-amino benzamide **1**, which has recently been tested in phase I clinical trials.

Experimental Section

Pharmacology. Both *in vitro* (receptor binding affinities) and *in vivo* (antagonism of apomorphine-induced mouse climbing, antagonism of apomorphine-induced stereotypy, and induction of catalepsy) activities of test compounds were determined by methods previously reported.[5]

Chemistry. General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole was prepared as previously reported.[5] Indazole-3-carboxylic acid (**47**) was prepared from commercially available isatin (**46**) as reported by Snyder.[18] Anhydrous solvents such as dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane, and toluene were obtained from Aldrich Chemical Co. in Sure/Seal bottles. All reactions involving air- or moisture-sensitive compounds were performed under an 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 eluant. 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, 75.43, or 125.706 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 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.

3-Azaisatoic Anhydride (9) and 6-Azaisatoic Anhydride (10). A 2:1 mixture of 3- and 6-azaisatoic anhydride (**9** and **10**, respectively) was obtained from 2,3-pyridinedicarboxylic anhydride (**7**) (11.4 g, 76 mmol), azidotrimethylsilane (11.4 mL, 86 mmol, 1.1 equiv), and $CHCl_3$ (50.0 mL) according to the method described by Le Count and Dewsbury.[8a] The precipitate obtained from the reaction mixture was filtered and dried to give 6.10 g (48%) of a 2:1 mixture of the title compounds as a white solid.[8b] Mp: 207−210 °C dec ^{1}H NMR data observed for the minor isomer (6-azaisatoic anhydride (**10**)) are given in square brackets. ^{1}H NMR (DMSO-d_6): δ 7.29 (dd, 1, J = 4.9, 7.8), [7.53 (dd, 1, J =1.5, 8.6)], [7.69 (dd, 1, J = 4.5, 8.6)], 8.29 (dd, 1, J = 1.8, 7.8), [8.49 (dd, 1, J = 1.5, 4.5)], 8.64 (dd, 1, J = 1.8, 4.9), [11.53 (br s, 1)], 12.53 (br s, 1).

4-Azaisatoic Anhydride (11) and 5-Azaisatoic Anhydride (12). Anhydrous $CHCl_3$ (50.0 mL), 3,4-pyridinedicarboxylic anhydride (**8**) (11.5 g, 77.1 mmol), and azidotrimethylsilane (10.1 g, 88.0 mmol, 1.14 equiv) were added to a 250-mL, round-bottomed flask and placed under N_2. The resulting creamy suspension was gently warmed to initiate the reaction. The reaction was exothermic, and nitrogen gas was evolved. After 10 min, the gas evolution subsided, and the solution was heated at reflux for 0.75 h. As the reaction proceeded, the solids dissolved to give a clear, pale yellow solution. The reaction mixture was allowed to cool to room temperature, and EtOH (4.5 mL, 77.1 mmol, 1.0 equiv) was added in one portion. Solids immediately precipitated out of solution upon this addition. The mixture was allowed to stir at room temperature for 15 min, and the solids were filtered, washed with $CHCl_3$, and dried in a vacuum oven at room temperature to give 12.6 g of a light yellow powder. This material was stirred with acetonitrile (100 mL), and the undissolved solids were filtered. The filtrate was heated at reflux for 0.5 h. The solution was allowed to cool to room temperature and cooled further in an ice bath. The solids that formed were filtered, and the filtrate was concentrated with a rotary evaporator to give 1.80 g of a yellow powder. A second crop of product was obtained by triturating all of the undissolved solids in boiling acetonitrile (100 mL) for 1.5 h. The mixture was filtered hot, and the filtrate was concentrated to provide an additional 3.35 g (41% total) of the title compounds as yellow solids. The crude product was a 1:1 mixture of 4- and 5-azaisatoic anhydride as indicated by integration of the corresponding signals in the ^{1}H NMR. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.08 (d, 1, J = 5.6), 7.80 (dd, 1, J = 4.8, 0.7), 8.45 (d, 1, J = 4.8), 8.54 (s, 1), 8.66 (d, 1, J = 5.6), 8.96 (s, 1), 12.08 (br s, 2). This material was used without further purification.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide Hydrochloride (13).** Picolinic acid (**3**) (1.2 g, 9.7 mmol) and potassium hydroxide (0.56 g, 10.0 mmol) were dissolved in distilled H_2O (25.0 mL). The H_2O was removed with a rotary evaporator, and the resulting white solid residue was treated with benzene (25.0 mL). The solution was concentrated and dried under high vacuum. The resulting potassium salt was suspended in benzene (15.0 mL) and cooled in an ice−water bath. Oxalyl chloride (1.0 mL, 11.5 mmol) was added dropwise to this cooled solution. The reaction mixture was allowed to warm to room temperature and slowly heated to a gentle reflux. The resulting wine-red/black solution was cooled and added dropwise to a cooled solution (ice−water bath) of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (3.0 g, 10.0 mmol) and triethylamine (2.5 mL, 17.9 mmol) in CH_2Cl_2 (10.0 mL). The reaction mixture was allowed to warm to room temperature and stir overnight. The dark suspension was concentrated with a rotary evaporator to give a black oil. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 5.01 g of a dark oil. The crude material was purified by flash chromatography on silica gel with a gradient eluant of $CHCl_3$ (100%)/$CHCl_3$−acetone−MeOH (28:2:1)/$CHCl_3$−acetone−MeOH (14:2:1) to give 1.80 g of the free amine. The product was taken up in CH_2Cl_2, treated with HCl (4.6 mL of a 1 N solution in Et_2O), and diluted with EtOAc. A dark precipitate was filtered from the solution, and the filtrate was allowed to stand for 3 days. The crystals that formed upon standing were filtered

and dried to give 1.15 g (27%) of the title compound as off-white crystals. Mp: 231−234 °C. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.76 (m, 2), 3.18−3.38 (m, 8), 3.57 (m, 2), 4.10 (m, 2), 7.47 (tm, 1, J = 7.6), 7.61 (m, 2), 8.02 (m, 2), 8.12 (t, 2, J = 8.1), 8.65 (dt, 1, J = 4.7, 1.2), 8.92 (t, 1, J = 6.2), 10.30 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.79, 27.54, 39.31, 47.51, 51.61, 56.32, 122.36, 123.02, 125.15, 125.78, 127.61, 128.10, 129.28, 138.94, 149.50, 151.16, 153.24, 163.37, 165.04. MS (CI/CH_4, 50 mA/s): M + 1, base (396). Anal. ($C_{21}H_{25}N_5OS$·HCl) C, H, N, S, Cl.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide Hydrochloride (14).** Nicotinoyl chloride hydrochloride (**5**) (1.1 g, 6.1 mmol) was added portionwise to an ice-cold, stirred solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.8 g, 6.0 mmol) and triethylamine (2.5 mL, 17.9 mmol, 3.0 equiv) in CH_2Cl_2 (25.0 mL). The resulting suspension was allowed to stir at 0 °C for 0.5 h and at room temperature for 2 h. The cloudy reaction mixture was diluted with CH_2Cl_2 (25.0 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator to give an off-white foam. The crude material was dissolved in 2-propanol (20.0 mL), chilled with an ice−water bath, and treated dropwise with HCl (6.0 mL of a 1 N solution in Et_2O) with swirling. The mixture was diluted with Et_2O (40.0 mL), and the resulting off-white solid was filtered and washed with Et_2O (3 × 10 mL). The salt was recrystallized from 95% EtOH to give 1.47 g (57%) of the title compound as off-white crystals. Mp: 229−231 °C. ^{1}H NMR (DMSO-d_6): δ 1.64 (m, 2), 1.81 (m, 2), 3.27 (m, 4), 3.47 (m, 2), 3.62 (br d, 2, J = 11.5), 4.10 (br d, 2, J = 13.1), 7.56 (m, 2), 7.62 (t, 1, J = 7.6), 8.14 (t, 2, J = 6.8), 8.23 (d, 1, J = 6.2), 8.73 (d, 1, J = 4.5), 8.81 (br t, 1, J = 6.2), 9.05 (s, 1), 10.82 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.76, 27.33, 39.58, 47.53, 51.61, 56.25, 122.35, 124.57, 125.16, 125.78, 128.11, 129.28, 131.10, 136.15, 149.55, 152.88, 153.26, 163.39, 165.92. MS (CI/CH_4, 50 mA/s): M + 1 (396). Anal. ($C_{21}H_{25}N_5OS$·HCl) C, H, N, S, Cl.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-pyridinecarboxamide Hydrochloride (15).** This compound was prepared according to the method described for compound **14**, by employing isonicotinoyl chloride hydrochloride (**6**) (1.1 g, 6.1 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.8 g, 6.0 mmol), and triethylamine (2.5 mL, 17.9 mmol, 3.0 equiv) in CH_2Cl_2 (25.0 mL). The crude hydrochloride salt was recrystallized from 95% EtOH to give 1.20 g (46%) of the title compound as off-white crystals. Mp: 238−240 °C. ^{1}H NMR (DMSO-d_6): δ 1.64 (m, 2), 1.80 (m, 2), 3.29 (m, 4), 3.46 (m, 2), 3.61 (br d, 2, J = 10.5), 4.10 (br d, 2, J = 10.5), 7.49 (t, 1, J = 7.6), 7.62 (t, 1, J = 7.6), 7.80 (d, 2, J = 5.8), 8.15 (t, 2, J = 6.7), 8.75 (d, 2, J = 5.8), 8.90 (br t, 1, J = 5.5), 10.80 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.76, 27.24, 39.68, 47.53, 51.61, 56.24, 122.36, 122.45, 125.17, 125.78, 128.11, 129.28, 142.56, 151.30, 153.26, 163.39, 165.78. MS (CI/CH_4, 50 mA/s): M + 1 (396). Anal. ($C_{21}H_{25}N_5OS$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-pyridinecarboxamide Hydrochloride (19) and 3-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-pyridinecarboxamide Hydrochloride (16). A 2:1 mixture of 3-azaisatoic anhydride (**9**) and 6-azaisatoic anhydride (**10**) (1.0 g, 6.1 mmol) was added to a stirred solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.8 g, 6.0 mmol) in THF (20.0 mL). The reaction mixture was allowed to stir under nitrogen at room temperature for 0.5 h. The solvent was removed with a rotary evaporator, and the resulting crude residue was purified by flash chromatography on silica gel with a gradient eluant of CH_2Cl_2 (100%)/CH_2Cl_2−MeOH (98.5:1.5)/CH_2Cl_2−MeOH (97:3)/CH_2Cl_2−MeOH (93:7) to give 1.48 g (91%) of 2-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide (**19**) as a foam and 0.54 g (66%) of 3-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-2-pyridinecarboxamide (**16**) as a foam. The hydrochloride salts of each isomer were prepared independently by dissolving the free amine in CH_2Cl_2 (20.0 mL), filtering, and treating the filtrate with 1 N ethereal HCl (1 equiv). The solutions were diluted with EtOAc and allowed to stir at room temperature for 1 h. The resulting white crystals were collected by filtration and dried in a vacuum oven to give the corresponding hydrochloride salts.

3-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-pyridinecarboxamide Hydrochloride (16). TLC: silica gel, MeOH/$CHCl_3$ (1:9), R_f = 0.47. Mp: 238−240 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.74 (m, 2), 3.30 (m, 8), 3.58 (m, 2), 4.08 (m, 2), 6.84 (br s, 2), 7.15 (dd, 1, J = 1.4, 8.4), 7.24 (dd, 1, J = 4.2, 8.4), 7.47 (tm, 1, J = 8.0), 7.60 (tm, 1, J = 8.0), 7.79 (dd, 1, J = 1.4, 4.2), 8.12 (t, 2, J = 8.2), 8.69 (br t, 1, J = 6.2), 10.40 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.77, 26.55, 37.68, 46.47, 50.56, 55.29, 121.27, 124.07, 124.53, 124.70, 127.02, 127.24, 128.19, 128.91, 135.49, 146.32, 152.17, 162.28, 167.56. MS (CI/CH_4, 50 mA/s): m/z M + 1 (411). Anal. ($C_{21}H_{26}N_6OS$·HCl) C, H, N, S, Cl.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-pyridinecarboxamide Hydrochloride (19). TLC: silica gel, MeOH/$CHCl_3$ (1:9), R_f = 0.25. Mp: 220−222 °C. ^{1}H NMR (DMSO-d_6): δ 1.59 (m, 2), 1.75 (m, 2), 3.32 (m, 8), 3.57 (m, 2), 4.08 (m, 2), 6.60 (dd, 1, J = 4.8, 7.7), 7.10 (s, 2), 7.47 (t, 1, J = 7.6), 7.60 (t, 1, J = 7.5), 7.93 (dd, 1, J = 0.8, 7.6), 8.07 (dd, 1, J = 1.3, 4.7), 8.12 (t, 2, J = 8.0), 8.54 (br t, 1, J = 5.5), 10.55 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.84, 26.30, 38.45, 46.62, 50.71, 55.38, 110.97, 111.59, 121.51, 124.32, 124.94, 127.28, 128.45, 138.10, 149.18, 152.47, 158.05, 162.58, 167.33. MS (CI/CH_4, 50 mA/s): M + 1 (411). Anal. ($C_{21}H_{26}N_6$-OS·HCl) C, H, N, S, Cl.

3-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4-pyridinecarboxamide Dihydrochloride Hydrate (18) and 4-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide Dihydrochloride (17). A 1:1 mixture of 4-azaisatoic anhydride (**11**) and 5-azaisatoic anhydride (**12**) (4.71 g, 28.7 mmol) was added to a stirred solution of 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (8.33 g, 28.7 mmol, 1.0 equiv) in anhydrous THF (40 mL). The reaction mixture was allowed to stir under N_2 at room temperature for 1 h. The solvent was removed with a rotary evaporator, and the resulting crude residue was purified by flash chromatography (2×) on silica gel, once with 5:95 MeOH−CH_2Cl_2 and 0.1% triethylamine as eluant and once with 3:97 MeOH−CH_2Cl_2 and 0.1% triethylamine as eluant, to give 3.11 g (26%) of 3-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-pyridinecarboxamide as a tan powder (TLC: silica gel, MeOH/CH_2Cl_2 (5:95), R_f = 0.44) and 2.99 g (24%) of 4-amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)-3-pyridinecarboxamide as an orange solid (TLC: silica gel, MeOH/CH_2Cl_2 (5:95), R_f = 0.32). The hydrochloride salts of each isomer were prepared independently by treatment with 1 N ethereal HCl. The salts were recrystallized from either EtOH/Et_2O or 95% EtOH/Et_2O/hexanes and dried in a vacuum oven.

4-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-pyridinecarboxamide Dihydrochloride (17). Mp: 122−130 °C (effervesces). ^{1}H NMR (DMSO-d_6): δ 1.64 (m, 2), 1.79 (m, 2), 3.07 (m, 2), 3.30 (m, 8), 3.74 (br s, 2), 6.93 (d, 1, J = 6.6), 7.48 (t, 1, J = 7.5), 7.61 (t, 1, J = 8.7), 8.12 (m, 1), 8.44 (br d, J = 2), 8.74 (s, 1), 8.97 (br t, 1, J = 5.6), 12.40 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.12, 26.07, 38.30, 46.95, 50.83, 55.51, 111.05, 111.14, 121.22, 124.07, 124.64, 127.06, 128.13, 141.52, 142.36, 152.11, 157.68, 162.50, 165.22. Anal. ($C_{21}H_{26}N_6OS$·2HCl) C, H, N.

3-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-4-pyridinecarboxamide Dihydrochloride Hydrate (18). Mp: 229−231 °C. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.83 (m, 2), 3.25 (m, 6), 3.55 (m, 4), 4.06 (br d, 2, J = 13.2), 7.46 (t, 1, J = 7.6), 7.59 (dt, 1, J = 8.1, 0.8), 8.04 (s, 2), 8.12 (t, 1, J = 8.1), 8.31 (s, 1), 9.24 (br t, 1, J = 4.4), 11.45 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.73, 26.05, 38.47, 46.54, 50.64, 55.26, 121.51, 124.32, 124.93, 126.48, 126.40, 127.02, 127.28, 128.44, 130.62, 146.83, 152.46, 162.59, 165.43. Anal. ($C_{21}H_{26}N_6OS$·2HCl·0.5H_2O) C, H, N, Cl, H_2O.

Methyl 4-((*tert*-Butoxycarbonyl)amino)-3-thiophenecarboxylate (22). Methyl 4-aminothiophene-3-carboxylate hydrochloride (**21**) (6.57 g, 33.9 mmol), 1,4-dioxane (25 mL), and 5% aqueous Na_2CO_3 (25 mL) were combined in a 500 mL, round-bottomed flask, and the mixture was cooled in an ice−

water bath. A solution of di-*tert*-butyl dicarbonate (18.6 g, 85.2 mmol, 2.51 equiv) in 1,4-dioxane (25 mL) was slowly added to the reaction mixture. The ice−water bath was removed, and the reaction mixture was allowed to stir at room temperature for 18 h. An additional portion of di-*tert*-butyl dicarbonate (3.86 g, 17.7 mmol, 0.52 equiv) in 1,4-dioxane (10 mL) was added, and the reaction mixture was stirred at room temperature for 26 h. The reaction mixture was transferred to a separatory funnel. Water and EtOAc were added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed twice with H_2O, dried over $MgSO_4$, filtered, and concentrated to give a red-brown liquid. The crude product was partially purified by flush chromatography with a gradient eluant of hexanes (100−95%):EtOAc (0−5%) to give a colorless liquid. The title compound precipitated upon standing to give 2.09 g (24%) of the desired product. Mp: 100−102 °C. ^{1}H NMR (DMSO-d_6, 60 °C): δ 1.48 (s, 9), 3.84 (s, 3), 7.53 (d, 1, J = 3.5), 8.32 (d, 1, J = 3.5), 9.01 (br s, 1). ^{13}C NMR ($CDCl_3$): δ 28.69, 52.27, 80.94, 107.74, 121.74, 132.96, 137.74, 153.49, 164.78. Anal. ($C_{11}H_{15}NO_4S$) C, H, N.

4-((*tert*-Butoxycarbonyl)amino)-3-thiophenecarboxylic Acid (23). Methyl 4-((*tert*-butoxycarbonyl)amino)-3-thiophenecarboxylate (**22**) (2.08 g, 8.08 mmol), 95% EtOH (40 mL), and 50% sodium hydroxide (10 mL) were added to a 500-mL, round-bottomed flask and heated at 45 °C for 1 h. The reaction mixture was allowed to cool to room temperature, and the pH was adjusted to pH = 2 by the addition of 1 N HCl. The reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give a white solid. The product was dried a second time, as described above, and dried in a vacuum oven to give 1.83 g (93%) of the title compound as a white solid. Mp: 167−168 °C (effervesces). ^{1}H NMR (DMSO-d_6): δ 1.50 (s, 9), 7.54 (br d, 1, J = 3.3), 8.32 (d, 1, J = 3.5), 9.31 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 28.85, 81.07, 108.30, 122.83, 134.94, 137.35, 152.89, 166.20. Anal. ($C_{10}H_{13}NO_4S$) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-((*tert*-butoxycarbonyl)amino)-3-thiophenecarboxamide Hydrochloride Hydrate (24).** 4-((*tert*-Butoxycarbonyl)amino)-3-thiophenecarboxylic acid (**23**) (1.49 g, 6.12 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.09 g, 7.20 mmol, 1.18 equiv), and anhydrous DMF (20 mL) were combined in a 500-mL, round-bottomed flask. A solution of 1,3-dicyclohexylcarbodiimide (1.60 g, 7.75 mmol, 1.27 equiv) in anhydrous DMF (5 mL) was added dropwise to the reaction mixture, and the solution was stirred under N_2 for 0.25 h. 1-Hydroxybenzotriazole hydrate (1.0 g, 7.40 mmol, 1.21 equiv) was added to the solution, and the reaction mixture was stirred under N_2 at room temperature for 2.75 days. The suspension was filtered, and the filtrate was concentrated to give an orange oil. The crude free base was dissolved in CH_2Cl_2, and the solution was transferred to a separatory funnel. The organic phase was washed with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with saturated NaCl, dried over $MgSO_4$, filtered, and concentrated to give an orange oil. The free base was partially purified by flash chromatography with CH_2Cl_2 followed by CH_2Cl_2−MeOH (96:4) as eluant to give a cloudy orange oil. The oil was dissolved in CH_2Cl_2, filtered, and concentrated to give a less cloudy orange oil. The crude free base was dissolved in EtOAc, filtered, and concentrated to give 2.73 g (86%) of the free base as a clear orange oil. A portion of the free base was converted to its hydrochloride salt and recrystallized from EtOH to give a pale beige solid. Mp: 116−119 °C. ^{1}H NMR (DMSO-d_6): δ 1.44 (s, 9), 1.60 (m, 2), 1.78 (m, 2), 3.29 (m, 6), 3.44 (tm, 2, J = 12.1), 3.57 (d, 2, J = 11.9), 4.05 (d, 2, J = 13.4), 7.45 (t, 1, J = 7.6), 7.49 (br s, 1), 7.58 (t, 1, J = 7.5), 8.09 (d, 1, J = 8.2), 8.12 (d, 1, J = 8.4), 8.35 (d, 1, J = 3.4), 8.82 (br t, 1, J = 5.6), 10.17 (s, 1), 10.63 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.58, 27.02, 28.89, 38.89, 47.36, 51.47, 56.06, 80.62, 107.69, 122.16, 124.85, 124.97, 125.59, 127.93, 129.09, 129.35, 137.81, 153.01, 153.09, 163.18, 164.89. Anal. ($C_{25}H_{33}N_5O_3S\cdot HCl\cdot H_2O$) C, H, N, H_2O.

2-Cyano-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)acetamide (26). 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.23 g, 7.69 mmol), cyanoacetic acid (**25**) (0.76 g, 8.93 mmol, 1.16 equiv), and DMF (20 mL) were added to a 250-mL, round-bottomed flask and stirred under N_2. A solution of 1,3-dicyclohexylcarbodiimide (1.86 g, 9.01 mmol, 1.17 equiv) in DMF (5 mL) was added dropwise to the reaction mixture. 1-Hydroxybenzotriazole hydrate (1.24 g, 9.18 mmol, 1.19 equiv) was added, and the reaction mixture was allowed to stir at room temperature under N_2 for 23 h. The suspension was filtered, and the solid was washed with DMF. The filtrate was concentrated to give an orange oil. The crude free base was dissolved in EtOAc and filtered. The filtrate was applied directly to a silica gel column and partially purified by flash chromatography with a gradient eluant of EtOAc (90−80%): MeOH (10−20%) to give 2.92 g of the crude product as an orange oil. The crude free base was dissolved in CH_2Cl_2 and washed with saturated K_2CO_3. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 1.93 g (70%) of the title compound as a pale beige solid. ^{1}H NMR ($CDCl_3$): δ 1.63 (br t, 4, J = 3.3), 2.47 (br t, 2, J = 6.7), 2.69 (br t, 4, J = 4.9), 3.36 (m, 2), 3.37 (s, 2), 3.57 (br t, 4, J = 4.9), 6.66 (br s, 1), 7.36 (ddd, 1, J = 1.2, 7.0, 8.1), 7.47 (ddd, 1, J = 1.2, 6.9, 8.2), 7.82 (dt, 1, J = 7.8, 1.1), 7.91 (dm, 1, J = 8.0).

Methyl 3-Aminobenzo[*b*]thiophene-2-carboxylate (28). This compound was prepared according to the method of Beck[13] by employing 2-nitrobenzonitrile (**27**) (50.0 g, 0.338 mol), methyl thioglycolate (33.2 mL, 36.4 g, 0.343 mmol, 1.11 equiv), DMF (400 mL), and aqueous KOH (37.4 g of KOH/187 mL of H_2O) to give 36.1 g (52%) of the title compound as a pale beige solid. Mp: 109−111 °C. (lit.[13] mp: 110−111 °C). ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3), 5.92 (br s, 2), 7.37 (ddd, 1, J = 1.3, 7.0, 8.2), 7.48 (ddd, 1, J = 1.5, 7.0, 8.2), 7.64 (ddd, 1, J = 0.8, 1.5, 8.0), 7.74 (ddd, 1, J = 0.8, 1.2, 8.0). ^{13}C NMR (DMSO-d_6): δ 51.52, 98.21, 121.82, 123.30, 123.90, 128.29, 131.50, 139.90, 148.96, 165.87.

3-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-2-thiophenecarboxamide Hydrochloride (29). 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.83 g, 9.75 mmol) and anhydrous $CHCl_3$ (50 mL) were added to a 250-mL, round-bottomed flask and stirred under N_2. Trimethylaluminum (2.0 M in toluene) (9.8 mL, 19.6 mmol, 2.01 equiv) was added slowly, and the solution was stirred at room temperature for 0.5 h. A solution of methyl 3-amino-2-thiophenecarboxylate (**20**) (1.66 g, 10.56 mmol, 1.08 equiv) in anhydrous $CHCl_3$ (25 mL) was added, and the reaction mixture was heated at 45−50 °C for 5 days. The reaction mixture was slowly added to cold aqueous 1 N HCl (100 mL). The pH of the mixture was adjusted to pH = 10 with saturated aqueous K_2CO_3, and the mixture was transferred to a separatory funnel. Chloroform was added to the separatory funnel, and the layers were separated. The organic layer was washed with H_2O (2 × 200 mL). The aqueous layers were combined and extracted with $CHCl_3$. The organic layers were combined, washed with saturated NaCl, dried over $MgSO_4$, filtered and concentrated to give 6.53 g of the crude product as a thin dark brown-orange oil. The free base was purified by flash chromatography with CH_2Cl_2 followed by CH_2Cl_2−MeOH (95:5) to give 1.32 g of a tan solid. The free base (1.23 g, 3.06 mmol) was dissolved in CH_2Cl_2, and 1 N ethereal HCl (3.06 mL, 1.0 equiv) was added. The hydrochloride salt was recrystallized from EtOH/H_2O to give 0.93 g (21%) of the title compound as a tan solid. Mp: 230−232 °C. ^{1}H NMR (DMSO-d_6): δ 1.54 (m, 2), 1.75 (m, 2), 3.26 (m, 6), 3.48 (m, 2), 3.61 (br d, 2, J = 11.1), 4.10 (br d, 2, J = 12.5), 6.42 (br s, 1), 6.60 (d, 1, J = 5.3), 7.40 (d, 1, J = 5.3), 7.55 (m, 2), 8.15 (br t, 2, J = 6.9), 10.51 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.65, 27.61, 38.86, 47.40, 51.48, 56.24, 102.19, 121.90, 122.16, 124.97, 125.62, 127.92, 128.59, 129.12, 153.06, 154.08, 163.18, 165.53. Anal. ($C_{20}H_{25}N_5OS_2\cdot HCl$) C, H, N.

4-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-thiophenecarboxamide Hydrochloride (30). *N*-(4-

(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-4-((*tert*-butoxycarbonyl)amino)-3-thiophenecarboxamide (**24**) (3.13 g, 6.07 mmol), trifluoroacetic acid (24 mL), anhydrous anisole (6.4 mL), and anhydrous $CHCl_3$ (50 mL) were combined in a 250-mL, round-bottomed flask and stirred under N_2 at room temperature for 20 min. Thin layer chromatography indicated that the reaction was complete. The reaction mixture was concentrated to give an orange liquid. The crude product was dissolved in CH_2Cl_2 and transferred to a separatory funnel. The organic phase was washed with saturated $NaHCO_3$ and separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give an orange liquid. The crude free base was purified by flash chromatography with CH_2Cl_2 followed by CH_2Cl_2−MeOH (96:4) as eluant to give 1.57 g of the free base as a pale orange oil. The free base 1.40 g (3.37 mmol) was dissolved in EtOAc, and 3.4 mL of 1 N ethereal HCl (1.0 equiv) was added. The hydrochloride salt was filtered and dried to give 1.01 g (37%) of the title compound as an off-white solid. Mp: 204−206 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.79 (m, 2), 3.00−3.80 (m, 10), 4.04 (m, 2), 5.80 (br s, 2), 6.10 (d, 1, J = 3.3), 7.49 (ddd, 1, J = 1.0, 7.0, 8.1), 7.62 (ddd, 1, J = 1.0, 7.0, 8.1), 8.03 (d, 1, J = 3.5), 8.15 (br t, 2, J = 6.8), 8.40 (br t, 1, J = 5.5). ^{13}C NMR (DMSO-d_6): δ 21.70, 27.29, 38.70, 47.46, 51.51, 56.16, 97.85, 122.18, 124.98, 125.59, 125.87, 127.93, 128.16, 129.09, 148.60, 153.06, 163.24, 165.04. Anal. ($C_{20}H_{25}N_5OS_2$·HCl) C, H, N.

2-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)-3-thiophenecarboxamide (31). 2-Cyano-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl)acetamide (**26**) (1.83 g, 5.12 mmol), 1,4-dithiane-2,5-diol (1.79 g, 11.8 mmol, 2.30 equiv), triethylamine (1.70 mL, 1.23 g, 12.2 mmol, 2.38 equiv), and EtOH (30 mL) were added to a 500-mL, round-bottomed flask and heated at 60−65 °C under a nitrogen atmosphere for 3 h. The oil bath was removed, and the reaction mixture was allowed to cool. Water and CH_2Cl_2 were added, and the reaction mixture was transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give a red-brown residue. The crude free base was partially purified by flash chromatography with a gradient eluant of EtOAc (100−98%):MeOH (0−2%) to give a partially solidified orange oil. The free base was dissolved in EtOAc and filtered. The filtrate was partially concentrated to give a suspension. The pale tan solid was filtered and dried to give 0.239 g (11%) of the title compound. Mp: 155−159 °C dec ^{1}H NMR ($CDCl_3$): δ 1.68 (br s, 4), 2.48 (br s, 2), 2.68 (br s, 4), 3.42 (m, 2), 3.58 (br s, 4), 5.84 (br s, 1), 6.07 (br s, 2), 6.23 (d, 1, J = 5.8), 6.71 (br d, 1, J = 5.8), 7.35 (ddd, 1, J = 1.1, 7.0, 8.1), 7.46 (ddd, 1, J = 1.1, 7.0, 8.1), 7.81 (d, 1, J = 8.2), 7.90 (d, 1, J = 8.2). ^{13}C NMR (DMSO-d_6): δ 23.80, 27.47, 38.26, 49.61, 52.53, 57.61, 105.69, 107.55, 121.09, 124.18, 124.22, 124.43, 127.40, 127.89, 152.06, 161.05, 163.52, 165.45. Anal. ($C_{20}H_{25}N_5OS_2$·0.15$C_4H_8O_2$) C, H, N.

3-Amino-*N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl)benzo[*b*]thiophene-2-carboxamide Hydrochloride (32). 3-(4-(4-Aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.6 g, 8.96 mmol) and anhydrous $CHCl_3$ (20 mL) were added to a 100-mL, round-bottomed flask and stirred under N_2. A solution of 2.0 M trimethylaluminum in toluene (4.6 mL, 9.2 mmol, 1.03 equiv) was slowly added to the reaction mixture, and the pale yellow solution was stirred under N_2 for 20 min. Another portion of trimethylaluminum (4.6 mL, 9.2 mmol, 1.03 equiv) was added to the reaction mixture. A solution of methyl 3-aminobenzo[*b*]thiophene-2-carboxylate (**28**) (1.86 g, 8.98 mmol, 1.0 equiv) in anhydrous $CHCl_3$ (10 mL) was added to the reaction mixture, and the mixture was stirred under N_2 at room temperature for 0.5 h. The golden yellow solution was heated at 40 °C for 4 days. The oil bath was removed, and the dark orange solution was allowed cool. To the slightly warm reaction mixture was slowly added 1 N HCl (50 mL). The acidic reaction mixture was heated at 40 °C for 0.5 h. The reaction mixture was allowed to cool, and saturated K_2CO_3 was added. The reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the crude product as an orange liquid. The free base was purified by flash chromatography with a gradient eluant of CH_2Cl_2 (100−95%): MeOH (0−5%) to give 1.14 g (27%) of the free base as an orange oil. The free base (1.05 g, 2.25 mmol) was dissolved in EtOAc, and 2.25 mL of 1 N ethereal HCl (1.0 equiv) was added. The hydrochloride salt was recrystallized from EtOH/H_2O to give 0.82 g (18%) of the title compound as a beige solid. Mp: 242−244 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.76 (m, 2), 3.10−3.50 (m, 8), 3.59 (br d, 2, J = 11.2), 4.08 (br d, 2, J = 13.4), 7.07 (br s, 2), 7.38 (ddd, 1, J = 1.1, 7.1, 8.1), 7.47 (tm, 2, J = 7.6), 7.60 (ddd, 1, J = 1.1, 7.1, 8.2), 7.68 (br t, 1, J = 5.6), 7.83 (d, 1, J = 7.7), 8.03 (d, 1, J = 7.9), 8.12 (t, 2, J = 8.3), 10.39 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.61, 27.61, 39.10, 47.33, 51.40, 56.16, 99.33, 122.16, 123.48, 123.94, 124.75, 124.98, 125.59, 127.93, 128.49, 129.08, 133.38, 137.89, 148.29, 153.09, 163.20, 166.12. Anal. ($C_{24}H_{27}N_5OS_2$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-8-quinolinecarboxamide Hydrochloride (35).** Anhydrous DMF (20 mL), 8-quinolinecarboxylic acid (**34**) (1.04 g, 6.01 mmol), 1-hydroxybenzotriazole hydrate (0.898 g, 6.65 mmol, 1.11 equiv), and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.75 g, 6.03 mmol, 1.0 equiv) were combined in a 250-mL, round-bottomed flask. The reaction mixture was cooled in an ice−water bath and stirred under N_2. A solution of 1,3-dicyclohexylcarbodiimide (1.37 g, 6.64 mmol, 1.10 equiv) in anhydrous DMF (12 mL) was added dropwise to the reaction mixture. The ice−water bath was removed, and the reaction mixture was stirred at room temperature for 20 h. The suspension was concentrated *in vacuo*, and the crude product was partitioned between EtOAc and saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give a mixture of finely dispersed solids in an orange oil. EtOAc was added to the mixture, and the suspension was filtered. The filtrate was concentrated to give 2.98 g of the crude product as an orange oil. The crude product was purified by flash chromatography with CH_2Cl_2, CH_2Cl_2−MeOH (99:1), and CH_2Cl_2−MeOH (97:3) as eluant. The appropriate fractions were combined, concentrated, redissolved in CH_2Cl_2, filtered, and concentrated to give 1.46 g of the free base as a yellow oil. The free base was dissolved in CH_2Cl_2, and 1 N ethereal HCl (3.28 mL, 1.0 equiv) was added. The solvent was removed *in vacuo*. The resulting hydrochloride salt was dissolved in MeOH, and the solution was filtered through fluted filter paper directly into rapidly stirred EtOAc. The suspension was filtered to give 0.265 g of the title compound as a pale beige solid. The filtrate was concentrated and recrystallized from MeOH to give a second crop (0.447 g) for a total yield of 0.712 g (25%). Mp: 187−189 °C. ^{1}H NMR (DMSO-d_6): δ 1.68 (m, 2), 1.91 (m, 2), 3.10−3.42 (m, 4), 3.56 (m, 6), 4.03 (br d, 2, J = 11.8), 7.43 (t, l, J = 7.5), 7.56 (t, l, J = 7.6), 7.65 (dd, 1, J = 4.3, 8.3), 7.72 (t, l, J = 7.7), 8.09 (t, 2, J = 7.7), 8.17 (d, 1, J = 8.1), 8.54 (dm, 2, J = 7.6), 9.09 (dd, 1, J = 1.4, 4.1), 10.87 (br t, l, J = 5.5), 11.55 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.24, 26.95, 38.85, 46.72, 50.82, 55.59, 121.52, 121.90, 124.35, 124.94, 126.66, 127.31, 128.44, 128.56, 129.67, 132.38, 132.72, 138.30, 144.99, 150.82, 152.43, 162.60, 165.41. Anal. ($C_{25}H_{27}N_5OS$·HCl) C, H, N.

2-(2,3-Dihydro-1*H*-indol-1-yl)glyoxyloyl Chloride (36). This compound was prepared according to the procedure described by Welstead *et al.*[15] with modifications. Oxalyl chloride (102.1 g, 0.804 mol) and anhydrous CH_2Cl_2 (400 mL) were added to a 2-L, 3-necked, round-bottomed flask. The flask was equipped with a mechanical stirrer, addition funnel, and N_2 inlet. A solution of indoline (**33**) (48.0 g, 0.403 mol) in anhydrous CH_2Cl_2 (350 mL) was added dropwise to the stirred reaction mixture over a 2-h period. The reaction mixture was stirred at room temperature for 3 h and then allowed to stand overnight. The resulting red-brown solution was concentrated, and Et_2O was added to the residue. The suspension was filtered, and the filtrate was concentrated to give 56.75 g (68%) of the acid chloride as a yellow-green solid. The crude acid chloride was used without further purification. ^{1}H NMR (DMSO-d_6): δ 3.19 (t, 2, J = 8.3), 4.17 (t, 2, J = 8.3), 7.12 (t,

1, J = 6.9), 7.24 (t, 1, J = 7.1), 7.33 (d, 1, J = 7.0), 8.01 (d, 1, J = 7.6). Anal. ($C_{10}H_7NO_2$) C, H, N.

Indoline-7-carboxylic Acid (37). Aluminum chloride (12.7 g, 95.2 mmol, 5.0 equiv) and 2-(2,3-dihydro-1*H*-indol-1-yl)glyoxyloyl chloride (**36**) (4.00 g, 19.1 mmol) were added to a 300-mL, round-bottomed flask equipped with a magnetic stir bar and N_2 inlet. The mixture was quickly heated to 100−120 °C and allowed to stir for 20 min. The oil bath was removed, and the mixture was allowed to cool to room temperature. The resulting solid was broken up with a spatula and added to ice−water (600 mL). The aqueous mixture was stirred for 1 h and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give an oily red residue. The residue was triturated with acetone and filtered to give 0.71 g (22%) of 4,5-dihydropyrrolo[3,2,1-*hi*,*l*]-indoline-1,2-dione as a red solid. Mp: 203−207 °C (lit.[15] mp: 206−208 °C). ^{1}H NMR (DMSO-d_6): δ 3.36 (t, 2, J = 7.9), 4.06 (t, 2, J = 7.9), 6.95 (t, 1, J = 7.5), 7.24 (d, 1, J = 7.6), 7.46 (d, 1, J = 7.1). ^{13}C NMR (DMSO-d_6): δ 31.35, 46.88, 113.03, 122.72, 124.74, 126.22, 134.16, 156.45, 160.67, 184.71. Anal. ($C_{10}H_7NO_2$) C, H, N, S, Cl.

A solution of sodium hydroxide (1.82 g in 20.2 mL of H_2O) and 4,5-dihydropyrrolo[3,2,1-*hi*,*l*]indoline-1,2-dione (1.0 g, 5.8 mmol) were combined in a 100-mL, round-bottomed flask and stirred at room temperature for 30 min. A solution of hydrogen peroxide (1.82 mL of 30% H_2O_2 in 18.2 mL of H_2O) was added dropwise, and the reaction mixture was allowed to stir for 3.5 h. The reaction mixture was transferred to a separatory funnel and washed with benzene. The aqueous layer was separated, the pH was adjusted to 6−7 by the addition of 1 N HCl, and the solution was extracted with $CHCl_3$. The pH of the aqueous layer was adjusted to 4−5 by the addition of 1 N HCl and the mixture extracted with an additional portion of $CHCl_3$. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give a gold-tan solid. The crude product was triturated with benzene:isooctane (3:1) to give 0.54 g (57%) of the title compound as a tan solid. Mp: 164−166 °C (lit.[15] mp: 164−168 °C). ^{1}H NMR (DMSO-d_6): δ 2.93 (t, 2, J = 8.6), 3.55 (t, 2, J = 8.6), 6.44 (t, 1, J = 7.0), 7.13 (d, 1, J = 6.9), 7.36 (d, 1, J = 7.5). ^{13}C NMR (DMSO-d_6): δ 28.19, 46.70, 107.95, 115.49, 128.14, 128.43, 131.26, 154.48, 168.73. Anal. ($C_9H_9NO_2$) C, H, N.

1,2,3,4-Tetrahydro-8-quinolinecarboxylic Acid (38). This compound was prepared according to the method described by Coppola,[14] by employing 8-quinolinecarboxylic acid (**34**) (1.73 g, 9.99 mmol), platinum oxide hydrate (0.182 g), and EtOH (30 mL). The mixture was hydrogenated on a Parr hydrogenator at 50 psi for 2 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated to give 1.76 g (99%) of the title compound as a pale yellow solid. Mp: 158−160 °C (lit.[14] mp: 165−167 °C). ^{1}H NMR (DMSO-d_6): δ 1.77 (quin, 2, J = 5.9), 2.69 (t, 2, J = 6.2), 3.33 (t, 2, J = 5.5), 6.36 (t, 1, J = 7.5), 7.00 (d, 1, J = 7.0), 7.54 (d, 1, J = 8.0). ^{13}C NMR (DMSO-d_6): δ 21.46, 28.33, 41.68, 109.59, 114.17, 122.73, 130.58, 134.54, 149.13, 171.24. Anal. ($C_{10}H_{11}NO_2$) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-2,3-dihydro-1*H*-indole-7-carboxamide Hydrochloride (39).** This compound was prepared according to the method described for compound **35** by employing indoline-7-carboxylic acid (**37**) (0.86 g, 5.27 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.60 g, 5.51 mmol, 1.05 equiv), 1-hydroxybenzotriazole hydrate (0.78 g, 5.77 mmol, 1.10 equiv), 1,3-dicyclohexylcarbodiimide (1.35 g, 6.54 mmol, 1.24 equiv), and anhydrous DMF. The reaction mixture was allowed to stir at room temperature for 24 h, and the solvent was removed *in vacuo*. EtOAc was added to the residue, and the mixture was filtered to remove the insoluble material. The filtrate was washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 3.12 g of the crude product as an orange oil. The crude material was purified by flash chromatography with EtOAc−MeOH (99:1) followed by EtOAc−MeOH (97:3) as eluant. The appropriate fractions were combined, concentrated, redissolved in CH_2Cl_2, filtered, and concentrated to give 0.96 g of the free base as an orange oil. The free base was dissolved in CH_2Cl_2, and 1.0 N ethereal HCl (2.2 mL, 1.0 equiv) was added. The solution was concentrated, and the hydrochloride salt was dissolved in MeOH. The solution was filtered, and the filtrate was slowly added to ethyl acetate. The resulting beige solid was filtered and dried to give 0.37 g (15%) of the title compound. Mp: 190−193 °C. ^{1}H NMR (DMSO-d_6): δ 1.57 (m, 2), 1.77 (m, 2), 2.93 (t, 2, J = 8.4), 3.24 (m, 8), 3.51 (m, 4), 4.06 (br d, 2, J = 13.3), 6.56 (t, 1, J = 7.5), 7.14 (d, 1, J = 7.1), 7.45 (m, 2), 7.58 (t, 1, J = 7.5), 8.11 (t, 2, J = 8.1), 8.29 (br t, 1, J = 5.4), 10.75 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.99, 26.76, 28.48, 38.31, 46.51, 46.74, 50.83, 55.53, 113.82 (br), 117.26 (br), 121.55, 124.35, 124.97, 125.42, 127.16, 127.30, 128.48, 131.94, 151.29 (br), 152.45, 162.56, 167.44. Anal. ($C_{24}H_{29}N_5OS\cdot1.2HCl$) C, H, N, Cl.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2,3,4-tetrahydro-8-quinolinecarboxamide Hydrochloride Hydrate (40).** This compound was prepared according to the method described for compound **35** by employing 1,2,3,4-tetrahydro-8-quinolinecarboxylic acid (**38**) (1.06 g, 5.98 mmol), 1-hydroxybenzotriazole hydrate (0.90 g, 6.66 mmol, 1.1 equiv), 1,3-dicyclohexylcarbodiimide (1.47 g, 7.12 mmol, 1.2 equiv), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.82 g, 6.27 mmol, 1.05 equiv), and anhydrous DMF. The reaction mixture was allowed to stir at room temperature for 18 h and concentrated *in vacuo*, and the crude product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The finely dispersed solids were filtered, and the filtrate was concentrated to give the crude free base. This material was purified by flash chromatography as described for compound **35**. The purified free base (2.28 g, 5.07 mmol) was dissolved in CH_2Cl_2, and 1 N ethereal HCl (5.07 mL, 1.0 equiv) was added. The solvent was removed *in vacuo*, and the resulting hydrochloride salt was dissolved in MeOH. The solution was filtered through a fluted filter paper directly into rapidly stirred EtOAc. The suspension was filtered to give 0.28 g (9%) of the title compound as an orange-beige solid. Mp: 138−142 °C. ^{1}H NMR (DMSO-d_6): δ 1.55 (m, 2), 1.77 (m, 4), 2.69 (t, 2, J = 6.0), 3.21 (m, 8), 3.47 (t, 2, J = 12.9), 3.56 (d, 2, J = 11.6), 4.05 (d, 2, J = 13.4), 4.46 (br s, 1), 6.44 (t, 1, J = 7.5), 6.96 (d, 1, J = 7.0), 7.37 (d, 1, J = 7.8), 7.46 (t, 1, J = 7.5), 7.58 (t, 1, J = 7.5), 8.11 (t, 2, J = 8.2), 8.32 (br t, 1, J = 5.3), 10.91 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.54, 21.86, 27.43, 28.27, 39.11, 41.75, 47.56, 51.64, 56.34, 115.14, 115.19, 122.37, 123.35, 125.15, 125,78, 127.35, 128.10, 129.29, 132.84, 146.19, 153.26, 163.35, 170.20. Anal. ($C_{25}H_{31}N_5OS\cdot1.5HCl\cdot0.35H_2O$) C, H, N, Cl, H_2O.

Benzimidazole-7-carboxylic Acid (42). This compound was prepared according to the method described by Moyer *et al.*[17] with modifications. 3-Nitroanthranilic acid (**41**) (1.3 g, 7.14 mmol) was dissolved in 0.1 N aqueous NaOH (80 mL) and reduced on a Parr hydrogenator over 10% Pd−C at 15 psi. After 4 h, the reaction mixture was filtered through a pad of Celite, and the pad was washed with distilled water. The pale yellow filtrate was acidified to pH ≈ 1 (pH paper) with concentrated HCl. The acidic filtrate was allowed to stand in the refrigerator overnight. Formic acid (96%, 1 mL) was added to the acidic filtrate, and the solution was heated at reflux for 2 h. Thin-layer chromatography (CH_2Cl_2−MeOH−HOAc, 90:9:1) indicated the reaction was incomplete. Formic acid (96%, 1 mL) was added to the reaction mixture, and the solution was heated at reflux for 1 h. The reaction mixture was allowed to cool to room temperature, and the suspension was filtered to give 0.553 g of a beige solid. The filtrate was concentrated, and the solid residue was triturated with warm water to give another 0.19 g of the desired product as a red-beige solid for a total crude yield of 0.743 g (64%). ^{1}H NMR and mass spectral data are consistent with those previously reported.[17] This material was used without further purification.

1*H*-Indole-7-carboxylic Acid (43). This compound was prepared according to the method described by Ikan and Rapaport[16] by employing indoline-7-carboxylic acid (**37**) (3.0 g, 18.4 mmol), 10% Pd on carbon (0.75 g), and xylenes (150 mL). The reaction mixture was heated for 4 h. The hot solution was filtered through a pad of Celite, and the filtrate was concentrated to give 1.55 g (52%) of the title compound as a red-beige solid. Mp: 202−204 °C (lit.[16] mp: 202 °C). ^{1}H

NMR (DMSO-d_6): δ 6.52 (dd, 1, J = 2.0, 3.0), 7.08 (t, 1, J = 7.7), 7.35 (t, 1, J = 2.8), 7.74 (dd, 1, J = 1.2, 7.5), 7.81 (d, 1, J = 7.9), 11.05 (s, 1), 12.98 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 101.80, 113.83, 118.70, 124.13, 125.97, 127.16, 129.61, 134.90, 168.31.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1*H*-benzimidazole-4-carboxamide Hydrochloride Hydrate (44).** This compound was prepared according to the procedure described for compound **35** by employing benzimidazole-7-carboxylic acid (**42**) (0.66 g, 4.07 mmol), 1-hydroxybenzotriazole hydrate (0.619 g, 4.58 mmol, 1.13 equiv), 1,3-dicyclohexylcarbodiimide (1.02 g, 4.94 mmol, 1.21 equiv), and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.26 g, 4.34 mmol, 1.07 equiv). After 4 h, the reaction mixture was filtered, and the filtrate was concentrated to give an orange residue. The crude product was dissolved in EtOAc and CH_2Cl_2, and the solution was washed with saturated $NaHCO_3$ (2×). The aqueous layers were combined and extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 2.47 g of an orange oil. The crude product was purified by flash chromatography with CH_2Cl_2−MeOH (93:7) as eluant to give 0.41 g of an off-white foam. The free base (0.39 g) was dissolved in CH_2Cl_2, and 0.90 mL of 1 N ethereal HCl (1.0 equiv) was added. The solvent was removed *in vacuo*, and the hydrochloride salt was dissolved in EtOH. The solution was filtered through fluted paper, and the filtrate was slowly added to Et_2O. The hydrochloride salt precipitated as a pale beige solid to give 0.230 g (12%) of the title compound. Mp: 125−128 °C (softens and shrinks). ^{1}H NMR (DMSO-d_6): δ 1.66 (m, 2), 1.81 (m, 2), 3.31 (m, 6), 3.48 (m, 2), 3.57 (m, 2), 4.06 (br d, 2, J = 12.3), 7.33 (t, 1, J = 7.9), 7.45 (tm, 1, J = 7.6), 7.58 (tm, 1, J = 7.6), 7.75 (d, 1, J = 7.9), 7.86 (d, 1, J = 7.6), 8.10 (t, 2, J = 8.3), 8.46 (s, 1), 9.91 (br s, 1), 10.20 (br s, 1), 13.05 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 20.74, 26.64, 38.19, 46.31, 50.45, 55.18 116.40 (br), 121.12, 121.70 (br), 121.99, 122.10, 123.95, 124.56, 126.91, 128.06, 134.70 (br), 138.70 (br), 142.81, 152.06, 162.17, 164.83. (+)APCIMS: M + 1, base (435). Anal. ($C_{23}H_{26}N_6OS$·HCl·0.40H_2O) C, H, N, Cl, H_2O.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1*H*-indole-7-carboxamide Hydrochloride (45).** This compound was prepared according to the method described for compound **35** by employing 1*H*-indole-7-carboxylic acid (**43**) (1.32 g, 8.19 mmol), 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (2.47 g, 8.51 mmol, 1.04 equiv), 1-hydroxybenzotriazole hydrate (1.20 g, 8.88 mmol, 1.08 equiv), 1,3-dicyclohexylcarbodiimide (1.87 g, 9.06 mmol, 1.1 equiv), and anhydrous DMF. The reaction mixture was allowed to stir at room temperature for 16 h, and the solvent was removed *in vacuo*. EtOAc was added to the residue, and the suspension was filtered. The filtrate was washed with saturated $NaHCO_3$, and the layers were separated. The organic layer was 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, EtOAc−MeOH (99:1), and EtOAc−MeOH (97:3) as eluant to give 3.27 g of the free base as a yellow oil. The hydrochloride salt was prepared and recrystallized from EtOH to give 1.66 g (43%) of the title compound as an off-white solid. Mp: 210−212 °C. ^{1}H NMR (DMSO-d_6): δ 1.63 (m, 2), 1.83 (m, 2), 3.21 (m, 4), 3.37 (m, 2), 3.53 (m, 4), 4.04 (br d, 2, J = 13.4), 6.46 (t, 1, J = 2.7), 7.04 (t, 1, J = 7.6), 7.33 (t, 1, J = 2.7), 7.45 (t, 1, J = 7.6), 7.57 (t, 1, J = 7.7), 7.69 (t, 2, J = 7.1), 8.10 (t, 2, J = 7.7), 8.66 (t, 1, J = 5.5), 11.13 (s, 1), 11.18 (br s, 1). ^{13}C NMR (DMSO-d_6): δ 21.05, 26.81, 38.47, 46.75, 50.82, 55.55, 101.28, 117.32, 118.39, 120.14, 121.54, 123.97, 124.35, 124.97, 126.90, 127.31, 128.47, 129.45, 134.53, 152.45, 162.57, 167.39. Anal. ($C_{24}H_{27}N_5OS$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1*H*-indazole-3-carboxamide Hydrochloride (49)**. This compound was prepared according to the method described for compound **35** by employing indazole-3-carboxylic acid[18] (**47**) (0.84 g, 5.18 mmol), 1-hydroxybenzotriazole hydrate (0.77 g, 5.70 mmol, 1.1 equiv), 1,3-dicyclohexylcarbodiimide (1.19 g, 5.77 mmol, 1.11 equiv), and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.44 g, 4.96 mmol, 0.96 equiv). The concentrated reaction mixture 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 to give a gold-yellow solid. The crude product was purified by flash chromatography with CH_2Cl_2 followed by CH_2Cl_2−MeOH (97:3) as eluant to give 1.14 g of the free base. The hydrochloride salt was prepared and recrystallized from EtOH/H_2O to give 0.54 g (23%) of the title compound as a pale yellow solid. Mp: >250 °C. ^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2), 1.78 (m, 2), 3.32 (m, 8), 3.57 (d, 2, J = 11.2), 4.06 (d, 2, J = 13.2), 7.21 (ddd, 1, J = 0.8, 7.0, 7.9), 7.39 (ddd, 1, J = 1.3, 6.9, 8.3), 7.45 (ddd, 1, J = 1.2, 7.0, 8.1), 7.58 (t, 2, J = 8.4), 8.10 (t, 2, J = 7.6), 8.16 (d, 1, J = 8.1), 8.49 (t, 1, J = 6.0), 10.45 (br s, 1), 13.60 (s, 1). ^{13}C NMR (DMSO-d_6): δ 21.02, 26.92, 38.02, 46.72, 50.82, 55.56, 111.01, 121.53, 121.81, 121.92, 122.26, 124.34, 124.96, 126.74, 127.31, 128.46, 138.59, 141.41, 152.45, 162.56, 162.72. (+) APCIMS: M + 1, base (435). Anal. ($C_{23}H_{26}N_6OS$·HCl) C, H, N.

***N*-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1*H*-indole-3-carboxamide Hydrochloride (50)**. This compound was prepared according to the method described for compound **35** by employing indole-3-carboxylic acid (**48**) (0.835 g, 5.18 mmol), 1-hydroxybenzotriazole hydrate (0.767 g, 5.68 mmol, 1.1 equiv), 1,3-dicyclohexylcarbodiimide (1.18 g, 5.71 mmol, 1.1 equiv), and 3-(4-(4-aminobutyl)-1-piperazinyl)-1,2-benzisothiazole (1.49 g, 5.14 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 3 days. The suspension was filtered, and the filtrate was concentrated. The crude product was partitioned between saturated $NaHCO_3$ and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to give 2.66 g of a tan residue. The free base was purified by flash chromatography with CH_2Cl_2−MeOH (95:5) as eluant to give 0.972 g of an off-white glass. The hydrochloride salt was prepared and recrystallized from EtOH/H_2O to give 0.457 g (19%) of the title compound as an off-white solid. Mp: >250 °C. ^{1}H NMR (DMSO-d_6): δ 1.58 (m, 2), 1.80 (m, 2), 3.27 (m, 6), 3.47 (t, 2, J = 13.0), 3.57 (br d, 2, J = 11.8), 4.05 (br d, 2, J = 13.4), 7.09 (m, 2), 7.40 (d, 1, J = 7.3), 7.45 (t, 1, J = 8.1), 7.58 (t, 1, J = 7.5), 8.08 (m, 5), 10.92 (br s, 1), 11.59 (s, 1). ^{13}C NMR (DMSO-d_6): δ 21.07, 27.07, 37.92, 46.78, 50.86, 55.56, 110.93, 112.11, 120.56, 121.33, 121.55, 122.09, 124.35, 124.97, 126.47, 127.30, 128.02, 128.48, 136.41, 152.45, 162.56, 165.01. (+)APCIMS: M + 1, base (434). Anal. ($C_{24}H_{27}N_5OS$·HCl) C, H, N.

Acknowledgment. The authors acknowledge the excellent technical assistance of Mr. Richard Harper in the determination of data obtained in the *in vivo* behavioral models and Ms. Flora Tang for the determination of the receptor binding data. We also thank Mr. Lee Schaller, Mr. Steve Garrett and Mr. Kevin Farley for their assistance in the purification or preparation of compounds **17**, **39**, **45**, and **50**, Dr. Gary Martin for obtaining the ^{13}C NMR data for compounds **16**−**19**, and Ms. Jane Saiers for proofreading this manuscript.

References

(1) (a) Norman, M. H.; Rigdon, G. C.; Navas, F., III; Hall, W. R. Structure-Activity Relationships of a Series of Substituted Benzamides: Potent D_2/5-HT_2 Antagonists and 5-HT_{1a} Agonists as Neuroleptic Agents. *J. Med. Chem.* **1996**, *39*, 1172−1188. (b) Norman, M. H.; Navas, F., III. Piperazine and Piperidine Derivatives and Their Use as Antipsychotics. PCT Int. Pat Appl. WO 93/16073, Aug. 19, 1993.

(2) Jones-Humble, S. A.; Durcan, M. J.; Norton, R. M.; Tang, F. L. M.; Russell, A. V.; Watson, M. J.; Gengo, P. J.; Morgan, P. F.; Wang, C. M.; Cox, R. F. Preclinical Neurochemical and Electrophysiological Profile of 1192U90, A Potential Antipsychotic. *Neuropsychopharmacology* **1996**, *15*, 217−230.

(3) (a) Jann, M. W. Clozapine. *Pharmacotherapy* **1991**, *11*, 179−195. (b) Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F. Pharmacology of Risperidone (R 64 766), A New Antipsychotic with Serotonin-S_2 and Dopamine-D_2 Antagonistic Properties. *J.*

Pharmacol. Exp. Ther. **1988**, *244*, 685−693. (c) Meltzer, H. Y.; Matsubara, S.; Lee, J. -C. Classification of Typical and Atypical Antipsychotic Drugs on the Basis of Dopamine D-1, D-2 and Serotonin$_2$ pK_i Values. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 238−246.

(4) Rigdon, G. C.; Norman, M. H.; Cooper, B. R.; Howard, J. L.; Boncek, V. M.; Faison, W. L.; Nanry, K. P.; Pollard, G. T. 1192U90 in Animal Tests That Predict Antipsychotic Efficacy, Anxiolysis, and Extrapyramidal Side Effects. *Neuropsychopharmacology* **1996**, *15*, 231−242.

(5) Norman, M. H.; Ridgon, G. C.; Navas, F., III; Cooper, B. R. Cyclic Benzamides as Mixed Dopamine D_2/Serotonin 5-HT_2 Receptor Antagonists: Potential Antipsychotic Agents. *J. Med. Chem.* **1994**, *37*, 2552−2563.

(6) Wingfield, H. N., Jr.; Harlan, W. R.; Hanmer, H. R. The Preparation of Nicotinyl Chloride *J. Am. Chem. Soc.* **1953**, *75*, 4364.

(7) Washburne, S. S.; Peterson, W. R., Jr.; Berman, D. A. Reaction of Trimethylsilyl Azide with Anhydrides and Imides. A New Uracil Synthesis via Nitrogen Insertion. *J. Org. Chem.* **1972**, *37*, 1738−1742.

(8) (a) Le Count, D. J.; Dewsbury, D. J. Synthesis of 3-Diethylamino-1-ethylisothiazolo[3,4-*b*]pyridinium Perchlorate and an Improved Route to 3-Azaisatoic Anhydride. *Synthesis* **1982**, *11*, 972−973. (b) LeCount and Dewsbury[8a] reported that 3-azaisatoic anhydride was obtained as the sole product when 2,3-pyridinecarboxylic anhydride was reacted with azidotrimethylsilane.

(9) ChemIntosh ^{13}C-Module version 1.1, SoftShell International, Ltd., 1600 Ute Ave, Grand Junction, CO 81501−4614.

(10) Basha, A.; Lipton, M.; Weinreb, S. M. A Mild General Method for Conversion of Esters to Amides. *Tetrahedron Lett.* **1977**, *48*, 4171−4174.

(11) Levin, J. I.; Turos, E.; Weinreb, S. M. An Alternative Procedure for the Aluminum Mediated Conversion of Esters to Amides. *Synth. Commun.* **1982**, *12*, 989−993.

(12) Walser, A.; Flynn, T.; Mason, C. Pentacyclic Triazolodiazepines as PAF-Antagonists. *J. Heterocycl. Chem.* **1991**, *28*, 1121−1125.

(13) Beck, J. R. A Direct Synthesis of Benzo[*b*]thiophene-2-carboxylate Esters Involving Nitro Displacement. *J. Org. Chem.* **1972**, *37*, 3224−3226.

(14) Coppola, G. M. Novel Heterocycles. I. Synthesis and Reactions of 6,7-Dihydro-1*H*,3*H*,5*H*-pyrido[3,2,1-*ij*][3,1]-benzoxazine-1,3-dione. *J. Heterocycl. Chem.* **1978**, *15*, 645−647.

(15) Welstead, W. J., Jr.; Moran, H. W.; Stauffer, H. F.; Turnbull, L. B.; Sancilio, L. F. Antiinflammatory Agents. 1. Synthesis and Antiinflammatory Activity of 2-Amino-3-benzoylphenylacetic Acid. *J. Med. Chem.* **1979**, *22*, 1074−1079.

(16) Ikan, R.; Rapaport, E. Synthesis in the Indole Series - III Preparation of 5-,6- and 7-Cyano and -Carboxyimidolines and -Indoles. *Tetrahedron* **1967**, *23*, 3823−3827.

(17) Moyer, M. P.; Weber, F. H.; Gross, J. L. Structure-Activity Relationships of Imidazo[4,5-*f*]quinoline Partial Structures and Analogues. Discovery of Pyrazolo[3,4-*f*]quinoline Derivatives as Potent Immunostimulants. *J. Med. Chem.* **1992**, *35*, 4595−4601.

(18) Snyder, H. R.; Thompson, C. B.; Hinman, R. L. The Synthesis of an Indazole Analogue of DL-Tryptophen. *J. Am. Chem. Soc.* **1952**, *74*, 2009−2012.

(19) Köhler, C.; Hall, H.; Ögren, S. O.; Gawell, L. Specific *in vitro* and *in vivo* binding of ^{3}H-Raclopride: A potent Substituted Benzamide Drug with High Affinity for Dopamine D_2 Receptors in the Rat Brain. *Biochem. Pharmacol.* **1985,** *34*, 2251−2259.

(20) Peroutka, S. J. Pharmacological Differentiation and Characterization of 5-HT_{1a}, 5-HT_{1b}, and 5-HT_{1c} Binding Sites in Rat Frontal Cortex. *J. Neurochem.* **1986**, *47*, 529−540.

(21) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. [^{3}H]Ketanserin (R 41 468), a Selective ^{3}H-Ligand for Serotonin$_2$ Receptor Binding Sites. Binding Properties, Brain Distribution, and Functional Role. *Mol. Pharmacol.* **1982**, *21*, 301−314.

(22) Meltzer, H. Y.; Matsubara, S.; Lee, J.-C. Classification of Typical and Atypical Antipsychotic Drugs on the Basis of Dopamine D_1, D_2 and Serotonin$_2$ pK_i Values. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 238−246.

(23) Costall, B.; Naylor, R. J.; Nohria, V. Climbing Behaviour Induced by Apomorphine in Mice: A Potential Model for the Detection of Neuroleptic Activity. *Eur. J. Pharmacol.* **1978**, *50*, 39−50.

(24) Fludzinski, P.; Evrard, D. A.; Bloomquist, W. E.; Lacefield, W. B.; Pfeifer, W.; Jones, N. D.; Deeter, J. B.; Cohen, M. L. Indazoles as Indole Bioisosteres: Synthesis and Evaluation of the Tropanyl Ester and Amide of Indazole-3-carboxylate as Antagonists at the Serotonin 5HT_3 receptor. *J. Med. Chem.* **1987**, *30*, 1535−1537.

JM9603375